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INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
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☐ *Additional inventors are being named on the____ separately numbered sheets attached hereto*

TITLE OF THE INVENTION (280 characters max)

SYNTHETIC PROCESS FOR TRANS-(1R,2R)-AMINOCYCLOHEXYL ETHER COMPOUNDS

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ENCLOSED APPLICATION PARTS *(check all that apply)*

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☐ Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT *(check one)*

☒ Applicant claims small entity status. See 37 CFR 1.27.

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Respectfully submitted,

SIGNATURE [signature]

Date 05 June 03

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REGISTRATION NO. (*if appropriate*) 26868

Docket Number: 14365 PRO

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USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

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P19SMALL/REV05

SYNTHETIC PROCESS FOR TRANS-(1*R*,2*R*)-AMINOCYCLOHEXYL ETHER COMPOUNDS

FIELD OF THE INVENTION

The present invention is generally directed toward a process for the preparation c stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexyl ether compounds as well as variou intermediates and substrates involved.

BRIEF DESCRIPTION OF THE DRAWINGS

Scheme 1 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexyl ether compound of formula (9).

Scheme 2A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (16).

Scheme 2B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (16).

Scheme 3A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (20).

Scheme 3B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (20).

Scheme 4 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexyl ether compound of formula (9).

Scheme 5A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (16).

Scheme 5B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (16).

Scheme 6A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (20).

Scheme 6B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (20).

Scheme 7 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexyl ether compound of formula (9).

Scheme 8A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (16).

Scheme 8B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (16).

Scheme 9A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (20).

Scheme 9B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (20).

Scheme 10 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexyl ether compound of formula (9).

Scheme 11A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (16).

Scheme 11B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (16).

Scheme 12A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (20).

Scheme 12B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (20).

Scheme 13 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexyl ether compound of formula (9).

Scheme 14A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (16).

Scheme 14B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (16).

Scheme 15A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (20).

Scheme 15B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (20).

Scheme 16 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexyl ether compound of formula (9).

Scheme 17A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (16).

Scheme 17B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (16).

Scheme 18A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (20).

Scheme 18B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (20).

Scheme 19B illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexyl ether compound of formula (16).

Scheme 20B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (20).

Scheme 21 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (7).

Scheme 22A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (16).

Scheme 22B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (18).

Scheme 23B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (22).

Scheme 24 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (6).

Scheme 25A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (14).

Scheme 26 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (4).

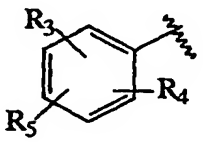
Scheme 27A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (13).

DESCRIPTION OF THE INVENTION

Definitions and Conventions

In the formulae depicted herein, a bond to a substituent and/or a bond that links a molecular fragment to the remainder of a compound may be shown as intersecting one or more bonds in a ring structure. This indicates that the bond may be attached to any one of the atoms that constitutes the ring structure, so long as a hydrogen atom could otherwise be present at that atom. Where no particular

substituent(s) is identified for a particular position in a structure, then hydrogen(s) is present at that position. For example, compounds of the invention containing the following group:



are intended to encompass groups wherein any ring atom that could otherwise be substituted with hydrogen, may instead be substituted with either R_3, R_4 or R_5, with the proviso that each of R_3, R_4 and R_5 appears once and only once on the ring. Ring atoms that are not substituted with any of R_3, R_4 or R_5 are substituted with hydrogen. In those instances where the invention specifies that a non-aromatic ring is substituted with more than one R group, and those R groups are shown connected to the non-aromatic ring with bonds that bisect ring bonds, then the R groups may be present at different atoms of the ring, or on the same atom of the ring, so long as that atom could otherwise be substituted with a hydrogen atom.

When the invention specifies the location of an asymmetric divalent radical, then that divalent radical may be positioned in any possible manner that provides a stable chemical structure.

A wavy bond from a substituent to the central cyclohexane ring indicates that that group may be located on either side of the plane of the central ring.

The compounds of the present invention contain at least two asymmetric carbon atoms and thus can exist as enantiomers and diastereomers. Unless otherwise noted, the phrase "stereoisomerically substantially pure" generally refers to those asymmetric carbon atoms that are described or illustrated in the structural formulae for that compound.

The phrase "independently at each occurrence" is intended to mean (i) when any variable occurs more than one time in a compound of the invention, the definition of that variable at each occurrence is independent of its definition at every other occurrence; and (ii) the identity of any one of two different variables (*e.g.*, R_1 within the set R_1 and R_2) is selected without regard of the identity of the other member of the set. However, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

In accordance with the present invention and as used herein, the following terms are defined to have following meanings, unless explicitly stated otherwise:

"Acid addition salts" refers to those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with

inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, or organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, salicylic acid and the like.

"Acyl" refers to branched or unbranched hydrocarbon fragments terminated by a carbonyl -(C=O)- group containing the specified number of carbon atoms. Examples include acetyl [$CH_3C(=O)$-, a C_2acyl] and propionyl [$CH_3CH_2C(=O)$-, a C_3acyl].

"Alkanoyloxy" refers to an ester substituent wherein the non-carbonyl oxygen is the point of attachment to the molecule. Examples include propanoyloxy [$(CH_3CH_2C(=O)$-O-, a C_3alkanoyloxy] and ethanoyloxy [$CH_3C(=O)$-O-, a C_2alkanoyloxy].

"Alkoxy" refers to an O-atom substituted by an alkyl group, for example, methoxy [$-OCH_3$, a C_1alkoxy].

"Alkoxyalkyl" refers to a alkylene group substituted with an alkoxy group. For example, methoxyethyl [$CH_3OCH_2CH_2$-] and ethoxymethyl ($CH_3CH_2OCH_2$-] are both C_3alkoxyalkyl groups.

"Alkoxycarbonyl" refers to an ester substituent wherein the carbonyl carbon is the point of attachment to the molecule. Examples include ethoxycarbonyl [$CH_3CH_2OC(=O)$-, a C_3alkoxycarbonyl] and methoxycarbonyl [$CH_3OC(=O)$-, a C_2alkoxycarbonyl].

"Alkyl" refers to a branched or unbranched hydrocarbon fragment containing the specified number of carbon atoms and having one point of attachment. Examples include *n*-propyl (a C_3alkyl), *iso*-propyl (also a C_3alkyl), and *t*-butyl (a C_4alkyl). Methyl is represented by the symbol Me or CH_3.

"Alkylene" refers to a divalent radical which is a branched or unbranched hydrocarbon fragment containing the specified number of carbon atoms, and having two points of attachment. An example is propylene [$-CH_2CH_2CH_2$-, a C_3alkylene].

"Alkylcarboxy" refers to a branched or unbranched hydrocarbon fragment terminated by a carboxylic acid group [-COOH]. Examples include carboxymethyl [HOOC-CH_2-, a C_2alkylcarboxy] and carboxyethyl [HOOC-CH_2CH_2-, a C_3alkylcarboxy].

"Aryl" refers to aromatic groups which have at least one ring having a conjugated pi electron system and includes carbocyclic aryl, heterocyclic aryl (also known as heteroaryl groups) and biaryl groups, all of which may be optionally substituted. Carbocyclic aryl groups are generally preferred in the compounds of the present invention, where phenyl and naphthyl groups are preferred carbocyclic aryl groups.

"Aralkyl" refers to an alkylene group wherein one of the points of attachment is to an aryl group. An example of an aralkyl group is the benzyl group (Bn) [$C_6H_5CH_2$-, a C_7aralkyl group].

"Cycloalkyl" refers to a ring, which may be saturated or unsaturated and monocyclic, bicyclic, or tricyclic formed entirely from carbon atoms. An example of a cycloalkyl group is the cyclopentenyl group (C_5H_7-), which is a five carbon (C_5) unsaturated cycloalkyl group.

"Carbocyclic" refers to a ring which may be either an aryl ring or a cycloalkyl ring, both as defined above.

"Carbocyclic aryl" refers to aromatic groups wherein the atoms which form the aromatic ring are carbon atoms. Carbocyclic aryl groups include monocyclic carbocyclic aryl groups such as phenyl, and bicyclic carbocyclic aryl groups such as naphthyl, all of which may be optionally substituted.

"Heteroatom" refers to a non-carbon atom, where boron, nitrogen, oxygen, sulfur and phosphorus are preferred heteroatoms, with nitrogen, oxygen and sulfur being particularly preferred heteroatoms in the compounds of the present invention.

"Heteroaryl" refers to aryl groups having from 1 to 9 carbon atoms and the remainder of the atoms are heteroatoms, and includes those heterocyclic systems described in "Handbook of Chemistry and Physics," 49th edition, 1968, R.C. Weast, editor; The Chemical Rubber Co., Cleveland, OH. See particularly Section C, Rules for Naming Organic Compounds, B. Fundamental Heterocyclic Systems. Suitable heteroaryls include furanyl, thienyl, pyridyl, pyrrolyl, pyrimidyl, pyrazinyl, imidazolyl, and the like.

"Hydroxyalkyl" refers to a branched or unbranched hydrocarbon fragment bearing an hydroxy (-OH) group. Examples include hydroxymethyl (-CH_2OH, a C_1hydroxyalkyl) and 1-hydroxyethyl (-$CHOHCH_3$, a C_2hydroxyalkyl).

"Thioalkyl" refers to a sulfur atom substituted by an alkyl group, for example thiomethyl (CH_3S-, a C_1thioalkyl).

"Modulating" in connection with the activity of an ion channel means that the activity of the ion channel may be either increased or decreased in response to administration of a compound or composition or method of the present invention. Thus, the ion channel may be activated, so as to transport more ions, or may be blocked, so that fewer or no ions are transported by the channel.

"Pharmaceutically acceptable carriers" for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remingtons Pharmaceutical Sciences, Mack Publishing Co. (A.R. Gennaro edit. 1985). For example, sterile saline and phosphate-buffered saline at physiological pH may be used. Preservatives, stabilizers, dyes and even flavoring agents may be provided

in the pharmaceutical composition. For example, sodium benzoate, sorbic acid and esters o *p*-hydroxybenzoic acid may be added as preservatives. Id. at 1449. In addition, antioxidants an suspending agents may be used. Id.

"Pharmaceutically acceptable salt" refers to salts of the compounds of the present invention derived from the combination of such compounds and an organic or inorganic acid (acid addition salts) or an organic or inorganic base (base addition salts). The compounds of the present invention may be used in either the free base or salt forms, with both forms being considered as being within the scope of the present invention.

The "therapeutically effective amount" of a compound of the present invention will depend on the route of administration, the type of warm-blooded animal being treated, and the physical characteristics of the specific warm-blooded animal under consideration. These factors and their relationship to determining this amount are well known to skilled practitioners in the medical arts. This amount and the method of administration can be tailored to achieve optimal efficacy but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize.

Compositions described herein as "containing a compound of the present invention" encompass compositions that may contain more than one compound of the present invention formula.

The synthetic procedures described herein, especially when taken with the general knowledge in the art, provide sufficient guidance to perform the synthesis, isolation, and purification of the compounds of the present invention.

The following examples are offered by way of illustration and not by way of limitation. Unless otherwise specified, starting materials and reagents may be obtained from well-known commercial supply houses, *e.g.*, Aldrich Chemical Company (Milwaukee, WI), and are of standard grade and purity; or may be obtained by procedures described in the art or adapted therefrom, where suitable procedures may be identified through the Chemical Abstracts and Indices therefor, as developed and published by the American Chemical Society.

Outline of Some General Reaction Processes of the Invention

The aminocyclohexyl ether compounds of the present invention contain ether and amino functional groups disposed in a 1,2 arrangement on a cyclohexane ring. Accordingly, the ether and amino functional groups may be disposed in either a *cis* or *trans* relationship, relative to one another and the plane of the cyclohexane ring. The present invention provides synthetic processes whereby compounds of

formula (9) with trans-(1*R*,2*R*) configuration for the ether and amino functional groups may be prepared in stereoisomerically substantially pure form. Compounds of formulae (18), (20), (22) and (24) are some of the examples represented by formula (9). The present invention also provides synthetic processes whereby compounds of formulae (4), (5), and (7) may be synthesized in stereoisomerically substantially pure forms. Compounds (13), (14), (17) and (16) are examples of formulae (4), (6), (7) and (7) respectively.

As outlined in Scheme 1, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (9) may be carried out by following a process starting from a monohalobenzene (1), wherein X may be F, Cl, Br or I.

In a first step, compound (1) is transformed by well-established microbial oxidation to the cis-cyclohexandienediol (2) in stereoisomerically substantially pure form (T. Hudlicky et al., Aldrichimica Acta, 1999, 32, 35; and references cited therein). In a separate step, compound (2) may be selectively reduced under suitable conditions to compound (3) (e.g. H_2-Rh/Al_2O_3; Boyd et al. JCS Chem. Commun. 1996, 45-46; Ham and Coker, J. Org. Chem. 1964, 29, 194-198; and references cited therein). In another separate step, the less hindered hydroxy group of formula (3) is selectively converted under suitable conditions into an activated form as represented by formula (4). An "activated form" as used herein means that the hydroxy group is converted into a good leaving group (–O–J) which on reaction with an appropriate nucleophile will result in a substitution product with inversion of the stereochemical configuration. The leaving group may be a mesylate (MsO-) group, a tosylate group (TsO-) or a nosylate (NsO-). The hydroxy group may also be converted into other suitable leaving groups according to procedures well known in the art. In a typical reaction for the formation of a tosylate, compound (4) is treated with a hydroxy activating reagent such as tosyl chloride (TsCl) in the presence of a base, such as pyridine or triethylamine. The reaction is generally satisfactorily conducted at about 0°C, but may be adjusted as required to maximize the yields of the desired product. An excess of the hydroxy activating reagent (e.g. tosyl chloride), relative to compound (4) may be used to maximally convert the hydroxy group into the activated form. In a separate step, transformation of compound (4) to compound (5) may be effected by hydrogenation and hydrogenolysis in the presence of a catalyst under appropriate conditions. Palladium on activated carbon is one example of the catalysts. Hydrogenolysis of alkyl or alkenyl halide such as (4) may be conducted under basic conditions. The presence of a base such as sodium ethoxide, sodium bicarbonate, sodium acetate or calcium carbonate is some possible examples. The base may be added in one portion or incrementally during the course of the reaction. In a separate step, alkylation of the free hydroxy group in compound (5) to form compound (7) is carried out under appropriate conditions

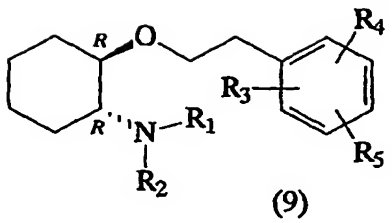
with compound (6), where –O–Q represents a good leaving group on reaction with a hydroxy function with retention of the stereochemical configuration of the hydroxy function in the formation of an ether compound. Trichloroacetimidate is one example for the –O–Q function. For some compound (6), it may be necessary to introduce appropriate protection groups prior to this step being performed. Suitable protecting groups are set forth in, for example, Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York NY (1991).

In a separate step, the resulted compound (7) is treated under suitable conditions with an amino compound of formula (8) to form compound (9) as the product. The reaction may be carried out with or without a solvent and at an appropriate temperature range that allows the formation of the product (9) at a suitable rate. An excess of the amino compound (8) may be used to maximally convert compound (7) to the product (9). The reaction may be performed in the presence of a base that can facilitate the formation of the product. Generally the base is non-nucleophilic in chemical reactivity. When the reaction has proceeded to substantial completion, the product is recovered from the reaction mixture by conventional organic chemistry techniques, and is purified accordingly. Protective groups may be removed at the appropriate stage of the reaction sequence. Suitable methods are set forth in, for example, Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York NY (1991).

The reaction sequence described above (Scheme 1) generates the compound of formula (9) as the free base. The free base may be converted, if desired, to the monohydrochloride salt by known methodologies, or alternatively, if desired, to other acid addition salts by reaction with an inorganic or organic acid under appropriate conditions. Acid addition salts can also be prepared metathetically by reaction of one acid addition salt with an acid that is stronger than that giving rise to the initial salt.

All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application is specifically and individually incorporated by reference.

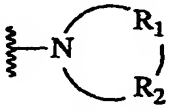
In one aspect, the present invention provides a process for the preparation of a stereoisomerically substantially pure compound of formula (9):



(9)

wherein, independently at each occurrence, R_1 and R_2 are independently selected from hydrogen, C_1-C_8alkyl, C_3-C_8alkoxyalkyl, C_1-C_8hydroxyalkyl, and C_7-C_{12}aralkyl; or

R_1 and R_2, when taken together with the nitrogen atom to which they are directly attached in formula (9), form a ring denoted by formula (I):



(I)

wherein the ring of formula (I) is formed from the nitrogen as shown as well as three to nine additional ring atoms independently selected from carbon, nitrogen, oxygen, and sulfur; where any two adjacent ring atoms may be joined together by single or double bonds, and where any one or more of the additional carbon ring atoms may be substituted with one or two substituents selected from hydrogen, hydroxy, C_1-C_3hydroxyalkyl, oxo, C_2-C_4acyl, C_1-C_3alkyl, C_2-C_4alkylcarboxy, C_1-C_3alkoxy, C_1-C_{20}alkanoyloxy, or may be substituted to form a spiro five- or six-membered heterocyclic ring containing one or two heteroatoms selected from oxygen and sulfur; and any two adjacent additional carbon ring atoms may be fused to a C_3-C_8carbocyclic ring, and any one or more of the additional nitrogen ring atoms may be substituted with substituents selected from hydrogen, C_1-C_6alkyl, C_2-C_4acyl, C_2-C_4hydroxyalkyl and C_3-C_8alkoxyalkyl; or

R_1 and R_2, when taken together with the nitrogen atom to which they are directly attached in formula (I), may form a bicyclic ring system selected from 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]hexan-3-yl, and 3-azabicyclo[3.2.0]heptan-3-yl; and

R_3, R_4 and R_5 are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, cyano, sulfamyl, trifluoromethyl, C_2-C_7alkanoyloxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_2-C_7alkoxycarbonyl, C_1-C_6thioalkyl, aryl and N(R_6,R_7) where R_6 and R_7 are independently selected from hydrogen, acetyl, methanesulfonyl, and C_1-C_6alkyl;

comprising the steps of starting with a monohalobenzene (1), wherein X may be F, Cl, Br or I; and following a reaction sequence as outlined in Scheme 1 under suitable conditions, wherein

–O–Q represents a good leaving group on reaction with a hydroxy function with retention of the stereochemical configuration of the hydroxy function in the formation of an ether compound; and

–O–J represents a good leaving group on reaction with a nucleophilic reactant with inversion of the stereochemical configuration as shown in Scheme 1 and all the formulae and symbols are as described above.

In another aspect, the present invention provides a process for the preparation of a stereoisomerically substantially pure compound of formula (18), comprising the steps under suitable conditions as shown in Scheme 2A, wherein all the formulae and symbols are as described above. As outlined in Scheme 2A, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (18) may be carried out by starting with a biotransformation of chlorobenzene (10) to compound (11) by microorganism such as *Pseudomonas putida* 39/D. Experimental conditions for the biotransformation are well established (Organic Synthesis, Vol. 76, 77 and T. Hudlicky et al., Aldrichimica Acta, 1999, 32, 35; and references cited therein). In a separate step, compound (11) is selectively reduced under suitable conditions to compound (12) (e.g. H_2-Rh/Al_2O_3; Boyd et al. JCS Chem. Commun. 1996, 45-46; Ham and Coker, J. Org. Chem. 1964, 29, 194-198; and references cited therein). In another separate step, the less hindered hydroxy group of formula (12) is selectively converted under suitable conditions into an activated form such as the tosylate (TsO-) of formula (13) (e.g. TsCl in the presence of pyridine). In a separate step, compound (13) is converted to compound (14) by reduction such as hydrogenation and hydrogenolysis in the presence of a catalyst under appropriate conditions. Palladium on activated carbon is one example of the catalysts. The reduction of compound (13) may be conducted under basic conditions e.g. in the presence of a base such as sodium ethoxide, sodium bicarbonate, sodium acetate or calcium carbonate. The base may be added in one portion or incrementally during the course of the reaction. In another separate step, the free hydroxy group in compound (14) is alkylated under appropriate conditions to form compound (16). The trichloroacetimidate (15) is readily prepared from the corresponding alcohol, 3,4-dimethoxyphenethyl alcohol which is commercially available (e.g. Aldrich), by treatment with trichloroacetonitrile. The alkylation of compound (14) by trichloroacetimidate (15) may be carried out in the presence of a Lewis acid such as HBF_4. In a separate step, the tosylate group of formula (16) is displaced by an amino compound such as 3*R*-pyrrolidinol (17) with inversion of configuration. 3*R*-pyrrolidinol (17) is commercially available (e.g. Aldrich) or may be prepared according to published procedure (e.g. Chem.Ber./Recueil 1997, 130, 385-397). The reaction may be carried out with or without a solvent and at an appropriate temperature range that allows the formation of the product (18) at a suitable rate. An excess of the amino compound (17) may be used to maximally convert

compound (16) to the product (18). The reaction may be performed in the presence of a base that can facilitate the formation of the product. Generally the additional base is non-nucleophilic in chemical reactivity. When the reaction has proceeded to substantial completion, the desired product is recovered from the reaction mixture by conventional organic chemistry techniques, and is purified accordingly.

The reaction sequence described above (Scheme 2A) in general generates the compound of formula (18) as the free base. The free base may be converted, if desired, to the monohydrochloride salt by known methodologies, or alternatively, to other acid addition salts by reaction with an inorganic or organic acid under appropriate conditions. Acid addition salts can also be prepared metathetically by reaction of one acid addition salt with an acid that is stronger than that giving rise to the initial salt.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (18) may be carried out under suitable conditions by a process as outlined in Scheme 2B, comprising the steps of starting from chlorobenzene (10) and following a reaction sequence analogous to the applicable portion (i.e. from compound (10) to compound (16)) that is described in Scheme 2A above leading to compound of formula (16). The latter is reacted under suitable conditions with an amino compound of formula (19) wherein Bn represents a benzyl protection group of the hydroxy function of 3*R*-pyrrolidinol to form compound (20). Compound (19) is commercially available (e.g. Aldrich) or may be prepared according to published procedure (e.g. Chem.Ber./Recueil 1997, 130, 385-397). The reaction may be carried out with or without a solvent and at an appropriate temperature range that allows the formation of the product (20) at a suitable rate. An excess of the amino compound (19) may be used to maximally convert compound (16) to the product (20). The reaction may be performed in the presence of a base that can facilitate the formation of the product. Generally the additional base is non-nucleophilic in chemical reactivity. The benzyl (Bn) protection group of compound (20) may be removed by standard procedure (e.g. hydrogenation in the presence of a catalyst under appropriate conditions. Palladium on activated carbon is one example of the catalysts. Other suitable conditions are as described in Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York NY (1991)). The product is a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (18) and is generally formed as the free base. The free base may be converted, if desired, to the monohydrochloride salt by known methodologies, or alternatively, if desired, to other acid addition salts by reaction with an inorganic or organic acids under appropriate conditions. Acid addition salts can also be prepared metathetically by reaction of one acid addition salt with an acid that is stronger than that giving rise to the initial salt.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (22) may be carried out under suitable conditions by a process as outlined in Scheme 3A, comprising the steps of starting from chlorobenzene (10) and following a reaction sequence analogous to the applicable portion that is described in Scheme 2A above leading to compound of formula (16). The latter is reacted with an amino compound of formula (21). Compound (21), 3*S*-pyrrolidinol, is commercially available (e.g. Aldrich) or may be prepared according to published procedure (e.g. Chem.Ber./Recueil 1997, 130, 385-397). The reaction may be carried out with or without a solvent and at an appropriate temperature range that allows the formation of the product (22) at a suitable rate. An excess of the amino compound (21) may be used to maximally convert compound (16) to the product (22). The reaction may be performed in the presence of a base that can facilitate the formation of the product. Generally the additional base is non-nucleophilic in chemical reactivity. The product is a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (22) and is formed as the free base. The free base may be converted, if desired, to the monohydrochloride salt by known methodologies, or alternatively, if desired, to other acid addition salts by reaction with an inorganic or organic acid under appropriate conditions. Acid addition salts can also be prepared metathetically by reaction of one acid addition salt with an acid that is stronger than that giving rise to the initial salt.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (22) may be carried out under suitable conditions by a process as outlined in Scheme 3B, comprising the steps of starting from chlorobenzene (10) and following a reaction sequence analogous to the applicable portion that is described in Scheme 2B above leading to compound of formula (16). The latter is reacted with an amino compound of formula (23) wherein Bn represents a benzyl protection group of the hydroxy function of 3*S*-pyrrolidinol to form compound (24). Compound (23) is commercially available (e.g. Aldrich) or may be prepared according to published procedure (e.g. Chem.Ber./Recueil 1997, 130, 385-397). The reaction may be carried out with or without a solvent and at an appropriate temperature range that allows the formation of the product (24) at a suitable rate. An excess of the amino compound (23) may be used to maximally convert compound (16) to the product (24). The reaction may be performed in the presence of a base that can facilitate the formation of the product. Generally the additional base is non-nucleophilic in chemical reactivity. The benzyl (Bn) protection group of compound (24) may be removed by standard procedure (e.g. hydrogenation in the presence of a catalyst under appropriate conditions. Palladium on activated carbon is one example of the catalysts. Other suitable conditions are as described in Greene, "Protective Groups in Organic Chemistry",

John Wiley & Sons, New York NY (1991)). The product is a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (22) and is generally formed as the free base. The free base may be converted, if desired, to the monohydrochloride salt by known methodologies, or alternatively, if desired, to other acid addition salts by reaction with an inorganic or organic acids under appropriate conditions. Acid addition salts can also be prepared metathetically by reaction of one acid addition salt with an acid that is stronger than that giving rise to the initial salt.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (9) may be carried out under suitable conditions by a process as outlined in Scheme 4, comprising the steps of starting with compound of formula (2) and following a reaction sequence analogous to the applicable portion that is described in Scheme 1, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (18) may be carried out under suitable conditions by a process as outlined in Scheme 5A, comprising the steps of starting with compound of formula (11) and following a reaction sequence analogous to the applicable portion that is described in Scheme 2A, wherein all the formulae and symbols are as described above. 3-Chloro-(1*S*,2*S*)-3,5-cyclohexadiene-1,2-diol of formula (11) is a commercially available product (e.g. Aldrich) or synthesized according to published procedure (e.g. Organic Synthesis, Vol. 76, 77 and T. Hudlicky et al., Aldrichimica Acta, 1999, 32, 35; and references cited therein).

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (18) may be carried out under suitable conditions by a process as outlined in Scheme 5B, comprising the steps of starting with compound of formula (11) and following a reaction sequence analogous to the applicable portion that is described in Scheme 2B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (22) may be carried out under suitable conditions by a process as outlined in Scheme 6A, comprising the steps of starting with compound of formula (11) and following a reaction sequence analogous to the applicable portion that is described in Scheme 3A, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (22) may be carried out under suitable conditions by a process as outlined in Scheme 6B, comprising the steps of starting with compound of formula (11) and following a reaction

sequence analogous to the applicable portion that is described in Scheme 3B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (9) may be carried out under suitable conditions by a process as outlined in Scheme 7, comprising the steps of starting with compound of formula (3) and following a reaction sequence analogous to the applicable portion that is described in Scheme 1, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (18) may be carried out under suitable conditions by a process as outlined in Scheme 8A, comprising the steps of starting with compound of formula (12) and following a reaction sequence analogous to the applicable portion that is described in Scheme 2A, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (18) may be carried out under suitable conditions by a process as outlined in Scheme 8B, comprising the steps of starting with compound of formula (12) and following a reaction sequence analogous to the applicable portion that is described in Scheme 2B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (22) may be carried out under suitable conditions by a process as outlined in Scheme 9A, comprising the steps of starting with compound of formula (12) and following a reaction sequence analogous to the applicable portion that is described in Scheme 3A, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (22) may be carried out under suitable conditions by a process as outlined in Scheme 9B, comprising the steps of starting with compound of formula (12) and following a reaction sequence analogous to the applicable portion that is described in Scheme 3B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (9) may be carried out under suitable conditions by a process as outlined in Scheme 10, comprising the steps of starting with compound of formula (4) and following a reaction sequence analogous to the applicable portion that is described in Scheme 1, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (18) may be carried out under suitable conditions by a process as outlined in Scheme 11A, comprising the steps of starting with compound of formula (13) and following a reaction sequence analogous to the applicable portion that is described in Scheme 2A, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (18) may be carried out under suitable conditions by a process as outlined in Scheme 11B, comprising the steps of starting with compound of formula (13) and following a reaction sequence analogous to the applicable portion that is described in Scheme 2B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (22) may be carried out under suitable conditions by a process as outlined in Scheme 12A, comprising the steps of starting with compound of formula (13) and following a reaction sequence analogous to the applicable portion that is described in Scheme 3A, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (22) may be carried out under suitable conditions by a process as outlined in Scheme 12B, comprising the steps of starting with compound of formula (13) and following a reaction sequence analogous to the applicable portion that is described in Scheme 3B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (9) may be carried out under suitable conditions by a process as outlined in Scheme 13, comprising the steps of starting with compound of formula (5) and following a reaction sequence analogous to the applicable portion that is described in Scheme 1, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (18) may be carried out under suitable conditions by a process as outlined in Scheme 14A, comprising the steps of starting with compound of formula (14) and following a reaction sequence analogous to the applicable portion that is described in Scheme 2A, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (18) may be carried out under suitable conditions by a process as outlined in

Scheme 14B, comprising the steps of starting with compound of formula (14) and following a reaction sequence analogous to the applicable portion that is described in Scheme 2B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (22) may be carried out under suitable conditions by a process as outlined in Scheme 15A, comprising the steps of starting with compound of formula (14) and following a reaction sequence analogous to the applicable portion that is described in Scheme 3A, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (22) may be carried out under suitable conditions by a process as outlined in Scheme 15B, comprising the steps of starting with compound of formula (14) and following a reaction sequence analogous to the applicable portion that is described in Scheme 3B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (9) may be carried out under suitable conditions by a process as outlined in Scheme 16, comprising the steps of starting with compound of formula (7) and following a reaction sequence analogous to the applicable portion that is described in Scheme 1, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (18) may be carried out under suitable conditions by a process as outlined in Scheme 17A, comprising the steps of starting with compound of formula (16) and following a reaction sequence analogous to the applicable portion that is described in Scheme 2A, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (18) may be carried out under suitable conditions by a process as outlined in Scheme 17B, comprising the steps of starting with compound of formula (16) and following a reaction sequence analogous to the applicable portion that is described in Scheme 2B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (22) may be carried out under suitable conditions by a process as outlined in Scheme 18A, comprising the steps of starting with compound of formula (16) and following a reaction

sequence analogous to the applicable portion that is described in Scheme 3A, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (22) may be carried out under suitable conditions by a process as outlined in Scheme 18B, comprising the steps of starting with compound of formula (16) and following a reaction sequence analogous to the applicable portion that is described in Scheme 3B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (18) may be carried out under suitable conditions by a process as outlined in Scheme 19B, comprising the steps of starting with compound of formula (20) and following a reaction sequence analogous to the applicable portion that is described in Scheme 2B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (22) may be carried out under suitable conditions by a process as outlined in Scheme 20B, comprising the steps of starting with compound of formula (24) and following a reaction sequence analogous to the applicable portion that is described in Scheme 3B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure compound of formula (7) may be carried out under suitable conditions by a process as outlined in Scheme 21, comprising the steps of starting with compound of formula (1) and following a reaction sequence analogous to the applicable portion that is described in Scheme 1, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure compound of formula (16) may be carried out under suitable conditions by a process as outlined in Scheme 22A, comprising the steps of starting with compound of formula (10) and following a reaction sequence analogous to the applicable portion that is described in Scheme 2A, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (20) may be carried out under suitable conditions by a process as outlined in Scheme 22B, comprising the steps of starting with compound of formula (10) and following a reaction sequence analogous to the applicable portion that is described in Scheme 2B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (24) may be carried out under suitable conditions by a process as outlined in Scheme 23B, comprising the steps of starting with compound of formula (10) and following a reaction sequence analogous to the applicable portion that is described in Scheme 3B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure compound of formula (5) may be carried out under suitable conditions by a process as outlined in Scheme 24, comprising the steps of starting with compound of formula (1) and following a reaction sequence analogous to the applicable portion that is described in Scheme 1, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure compound of formula (14) may be carried out under suitable conditions by a process as outlined in Scheme 25A, comprising the steps of starting with compound of formula (10) and following a reaction sequence analogous to the applicable portion that is described in Scheme 2A, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure compound of formula (4) may be carried out under suitable conditions by a process as outlined in Scheme 26, comprising the steps of starting with compound of formula (1) and following a reaction sequence analogous to the applicable portion that is described in Scheme 1, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure compound of formula (13) may be carried out under suitable conditions by a process as outlined in Scheme 27A, comprising the steps of starting with compound of formula (10) and following a reaction sequence analogous to the applicable portion that is described in Scheme 2A, wherein all the formulae and symbols are as described above.

In another aspect, the present invention provides a compound of formula (4), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above.

In another aspect, the present invention provides a compound of formula (5), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above.

In another aspect, the present invention provides a compound of formula (6), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above with the proviso that R_3, R_4 and R_5 cannot all be hydrogen.

In another aspect, the present invention provides a compound of formula (7), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above with the proviso that when R_3, R_4 and R_5 are all hydrogen then J is not a methanesulfonyl group.

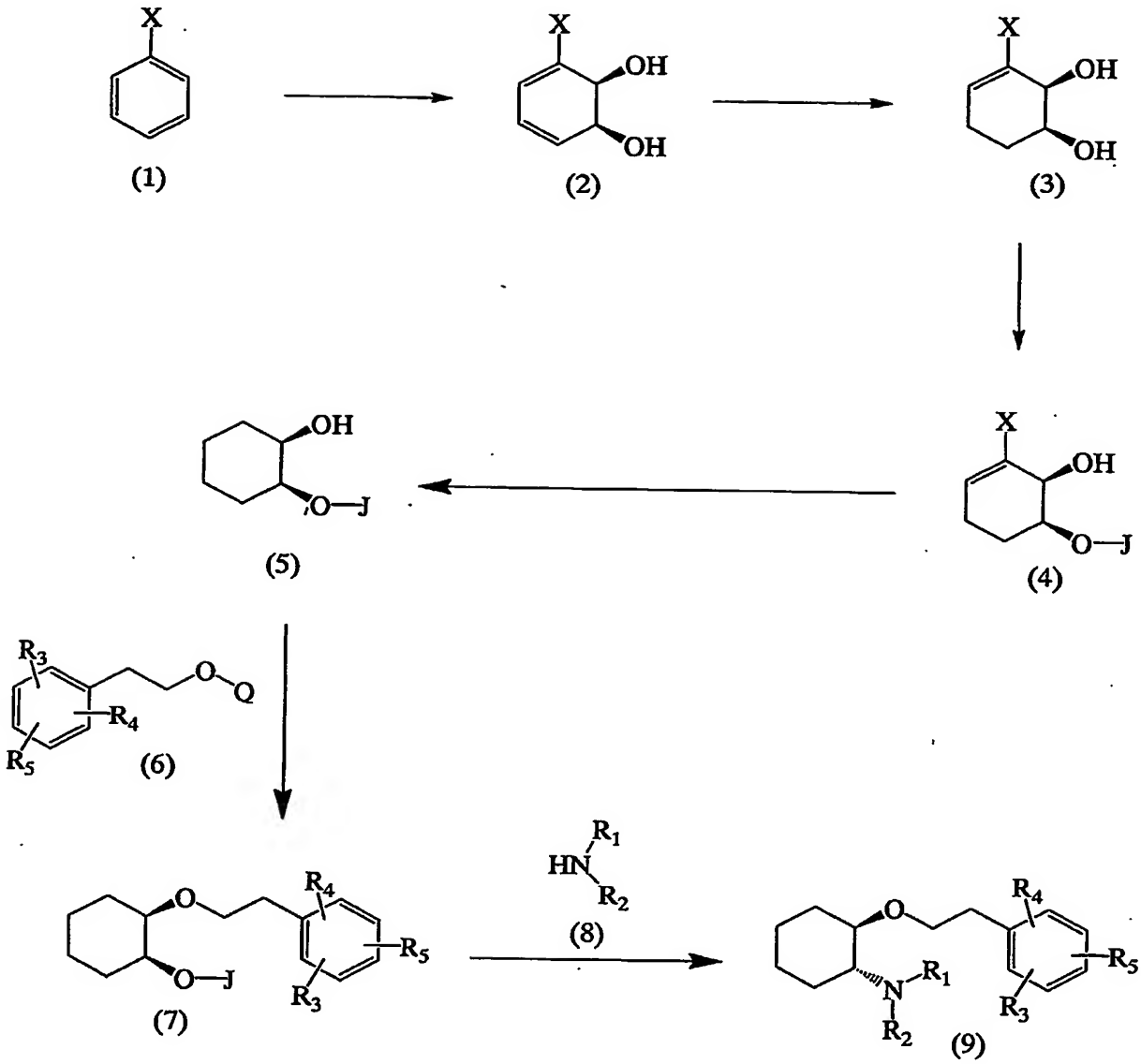
In another aspect, the present invention provides a compound of formula (13), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above.

In another aspect, the present invention provides a compound of formula (14), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above.

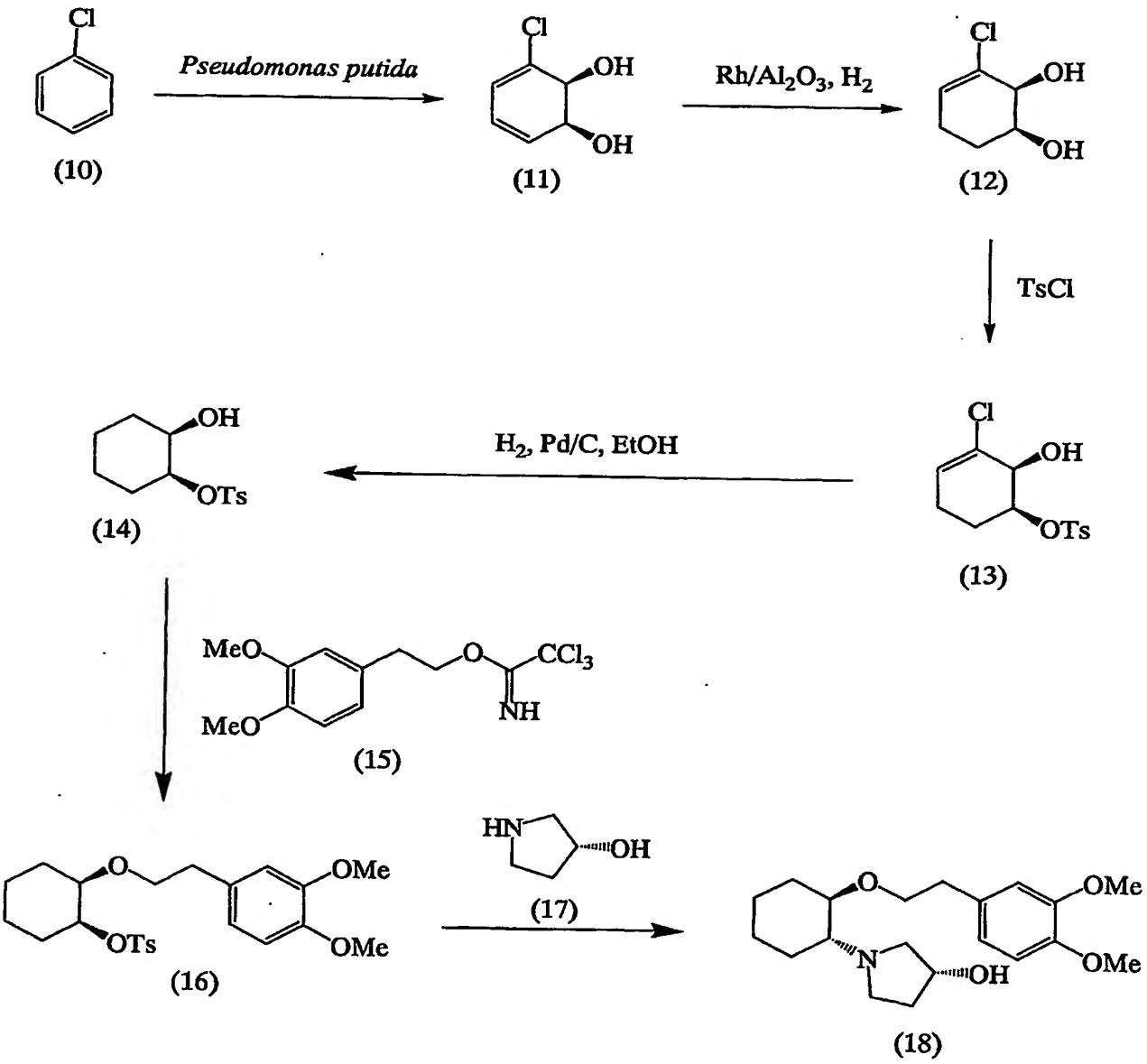
In another aspect, the present invention provides a compound of formula (16), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above.

In another aspect, the present invention provides a compound of formula (20), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above.

Scheme 1



Scheme 2A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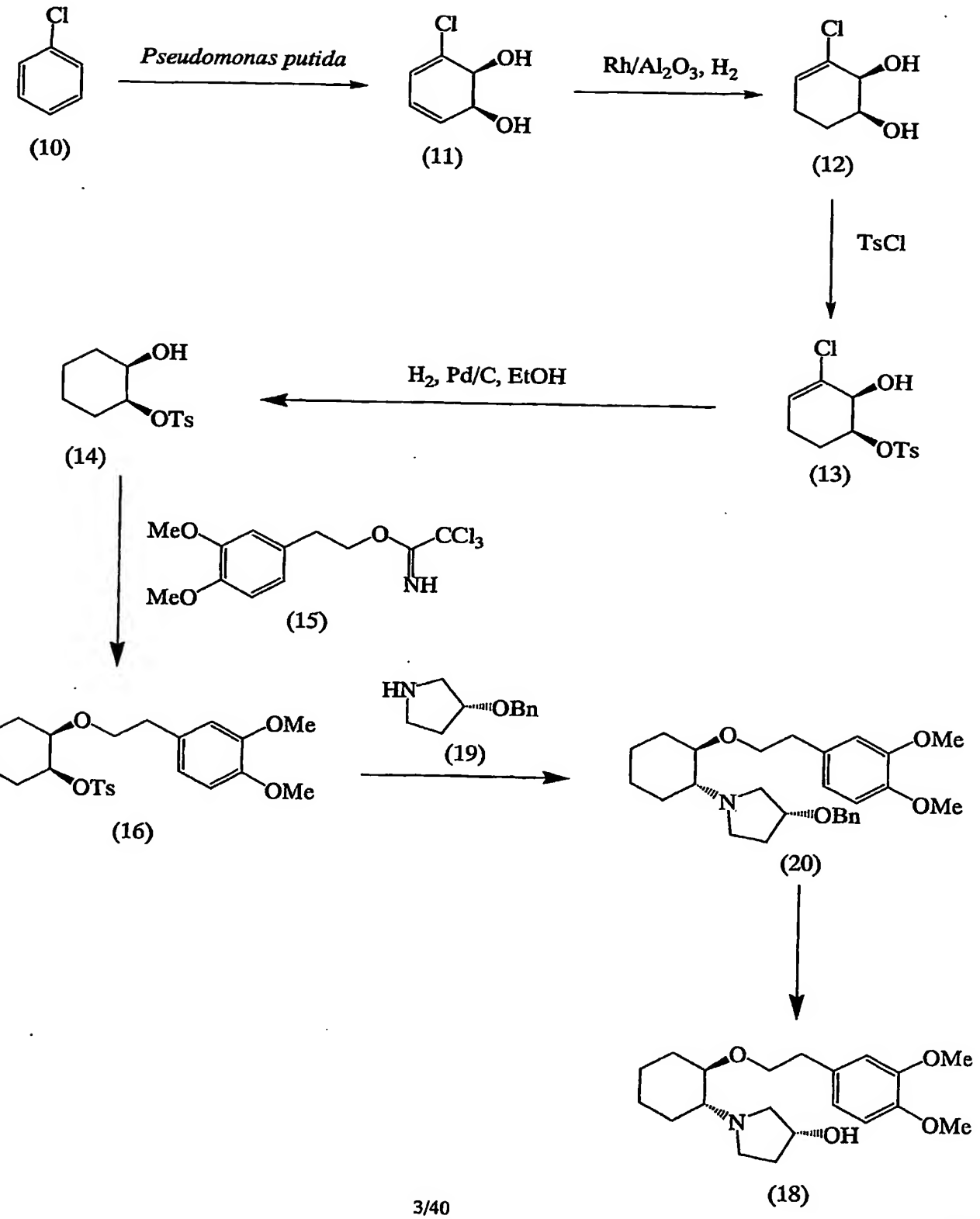
(18)

Scheme 2B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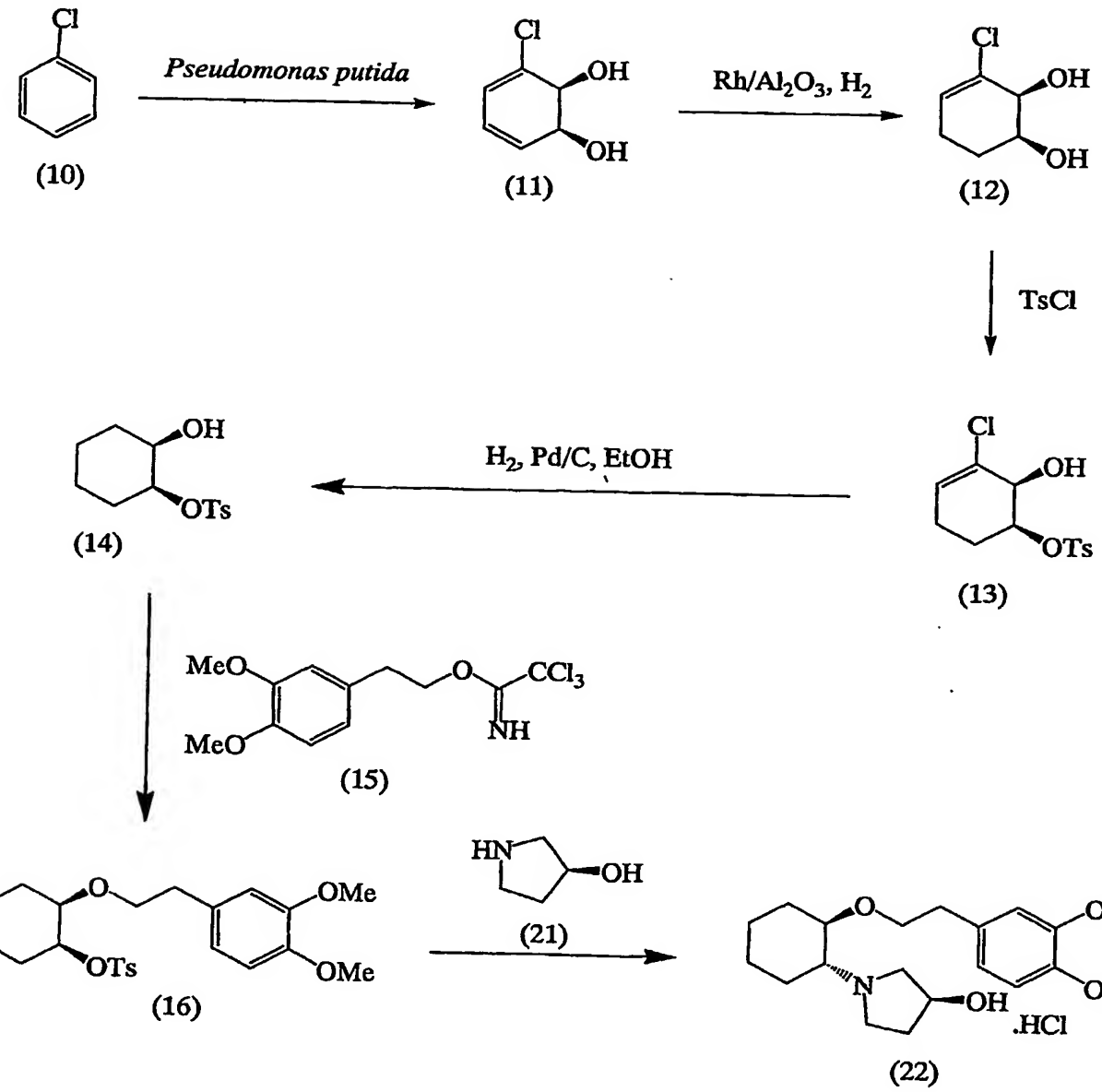
(18)

Scheme 3A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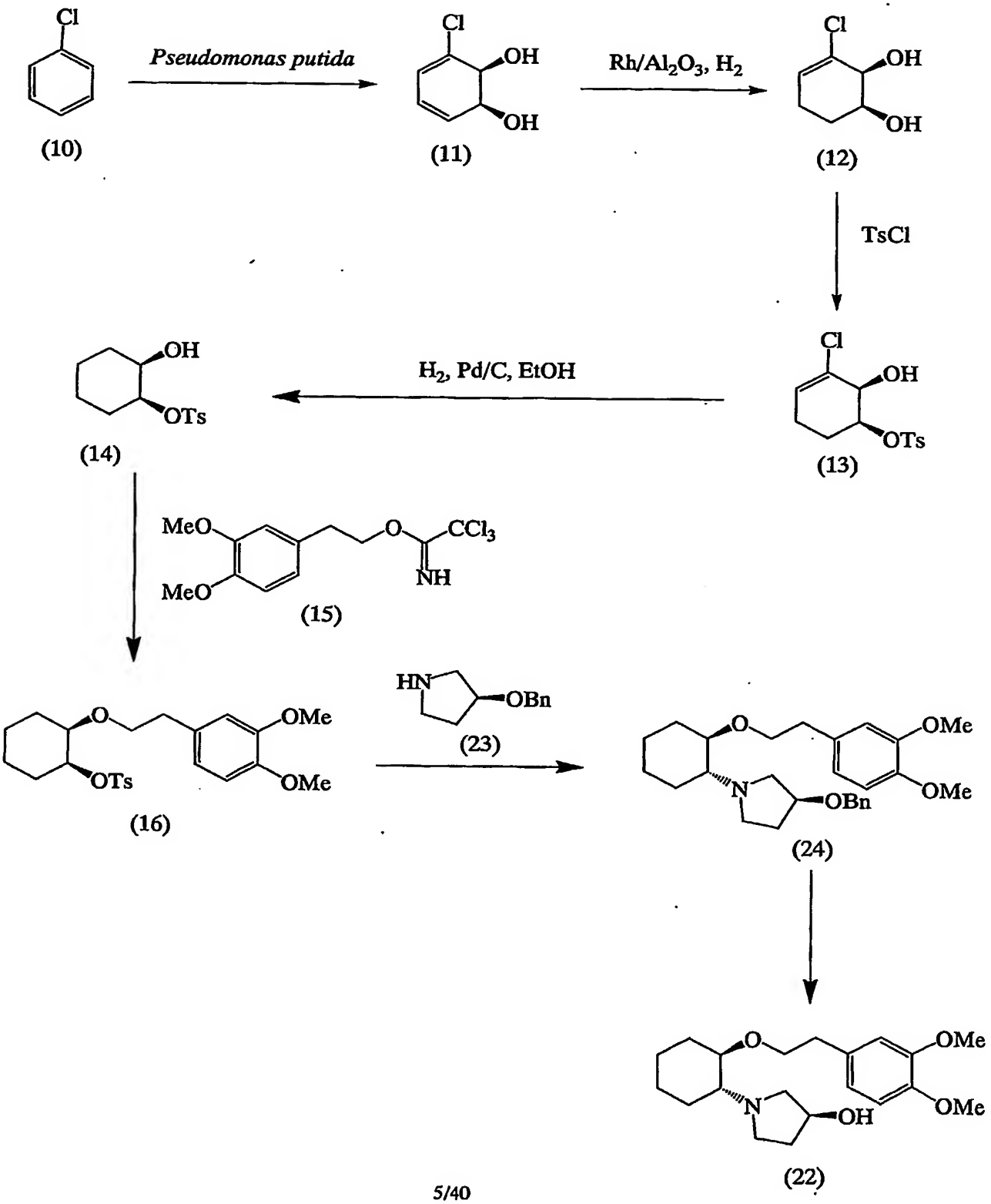
(22)

Scheme 3B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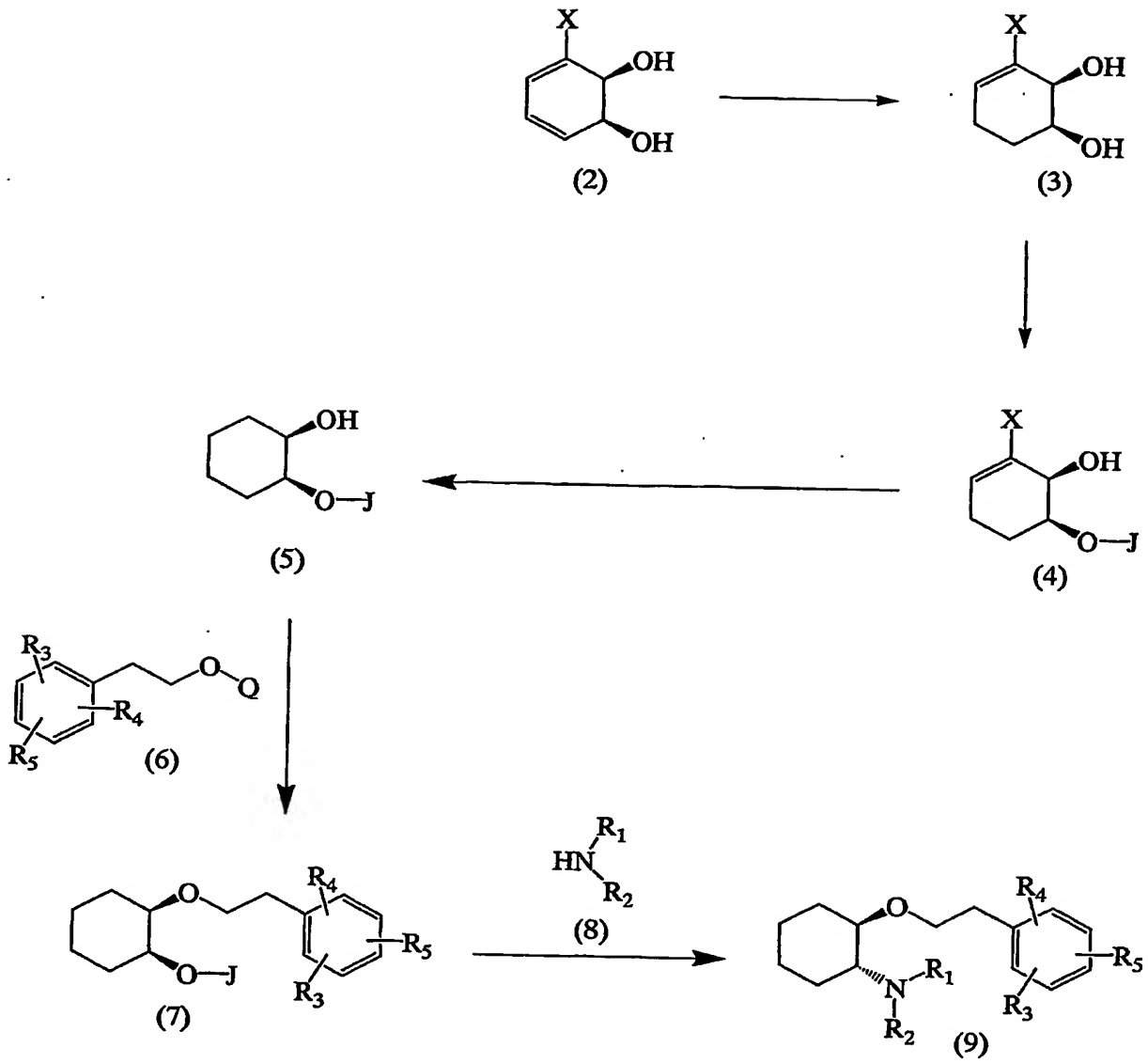
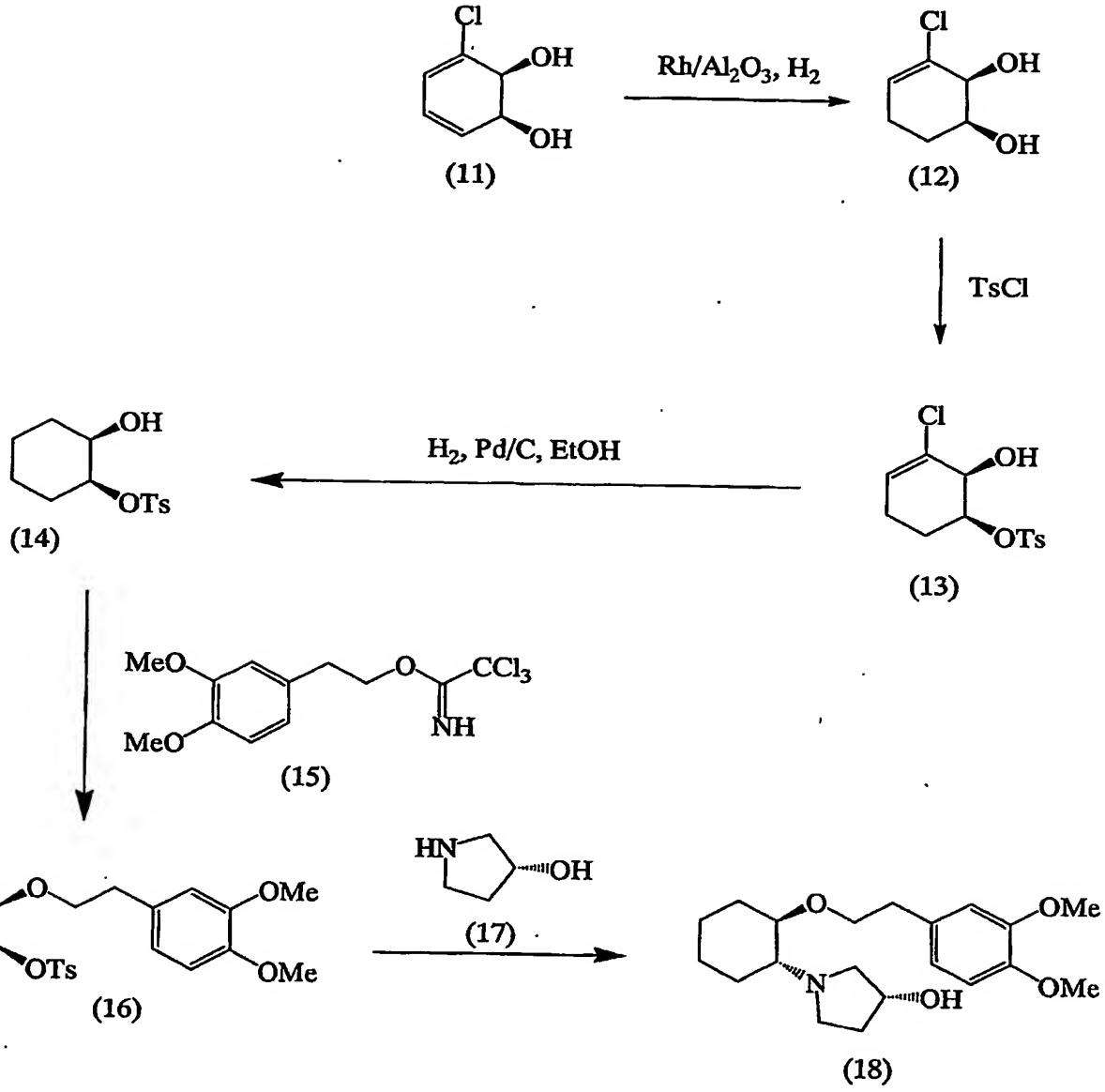
Scheme 4



Scheme 5A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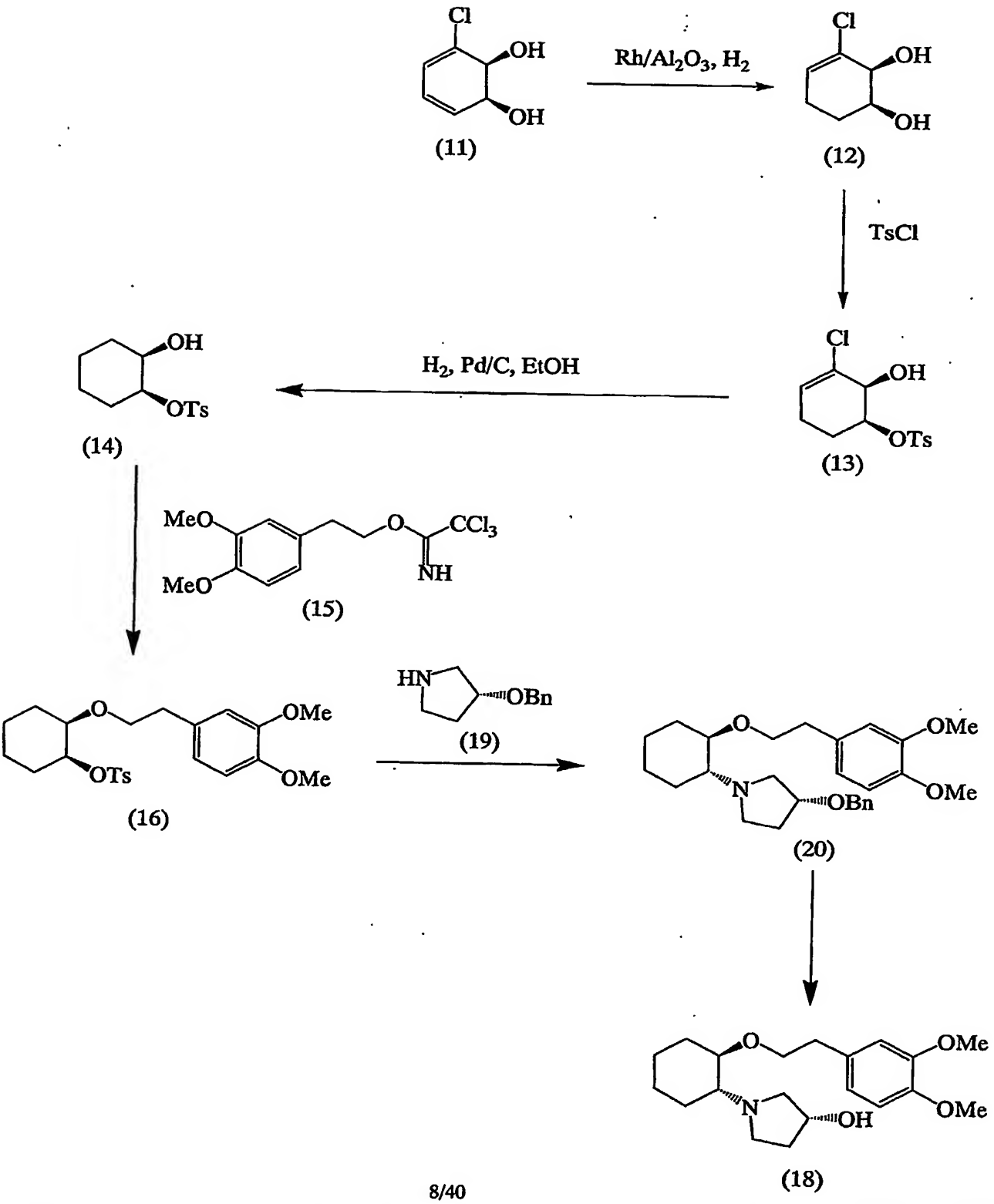
(18)

Scheme 5B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OTs
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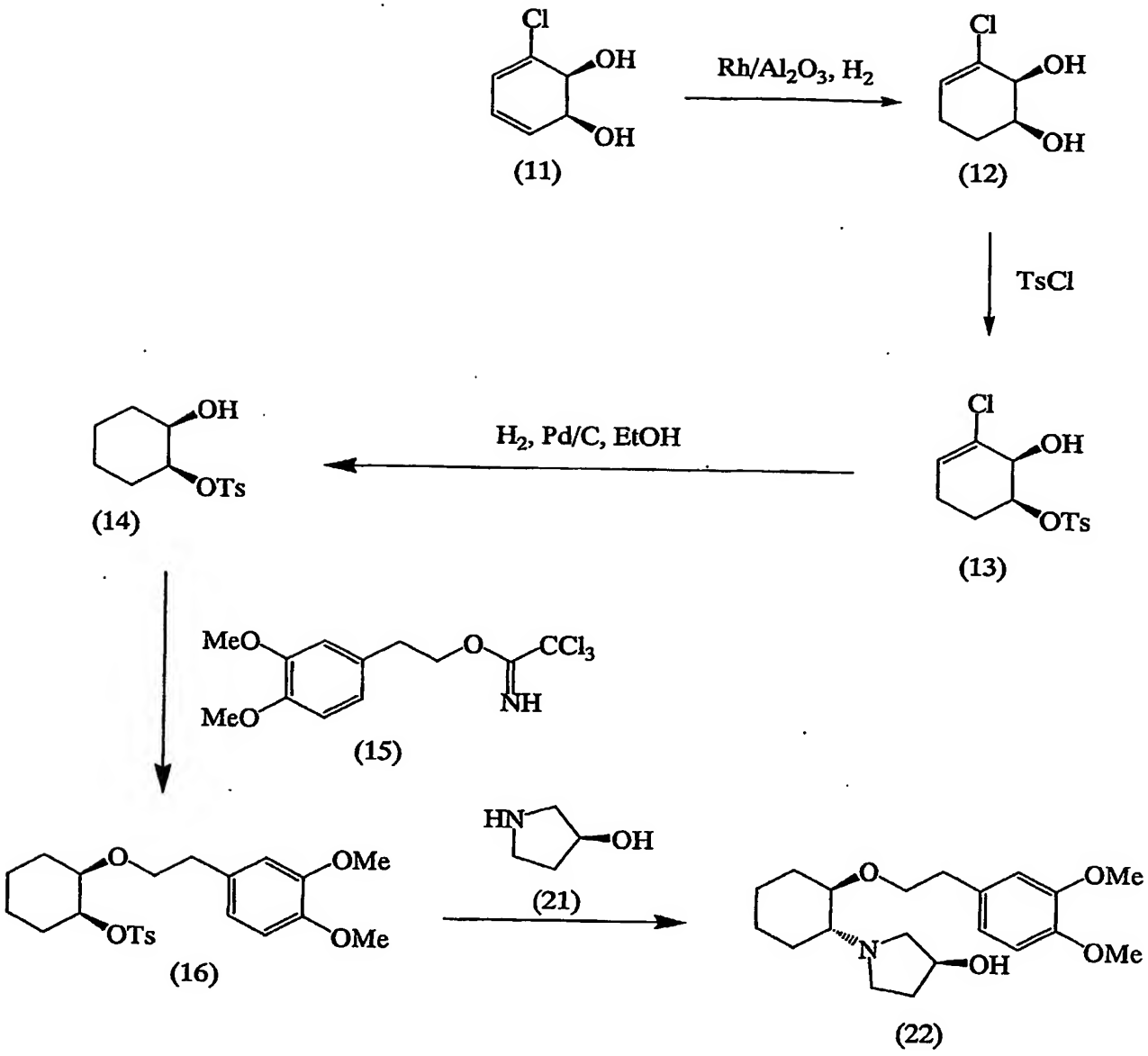
(18)

Scheme 6A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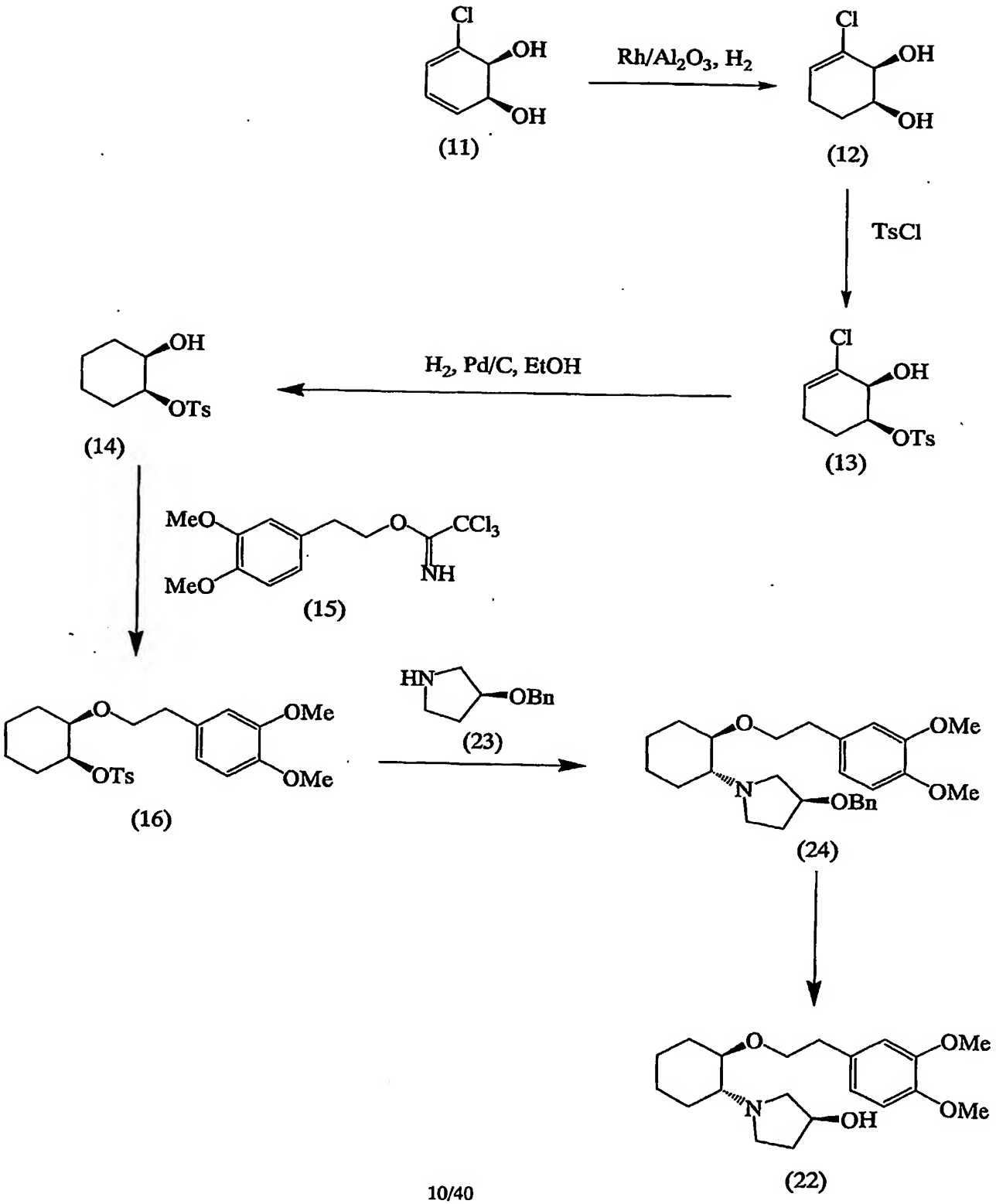
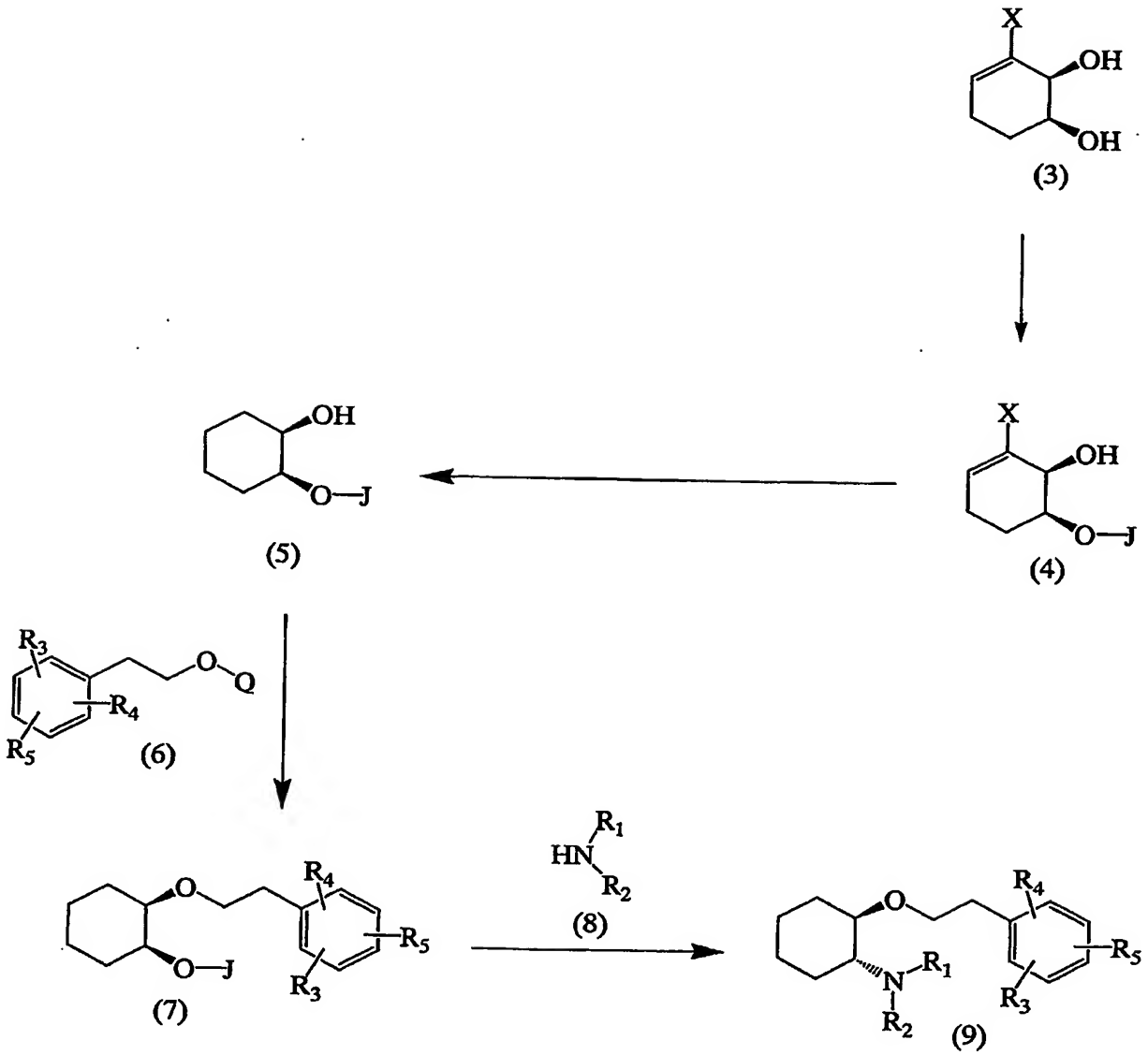
OMe
N
OH
OMe
(22)

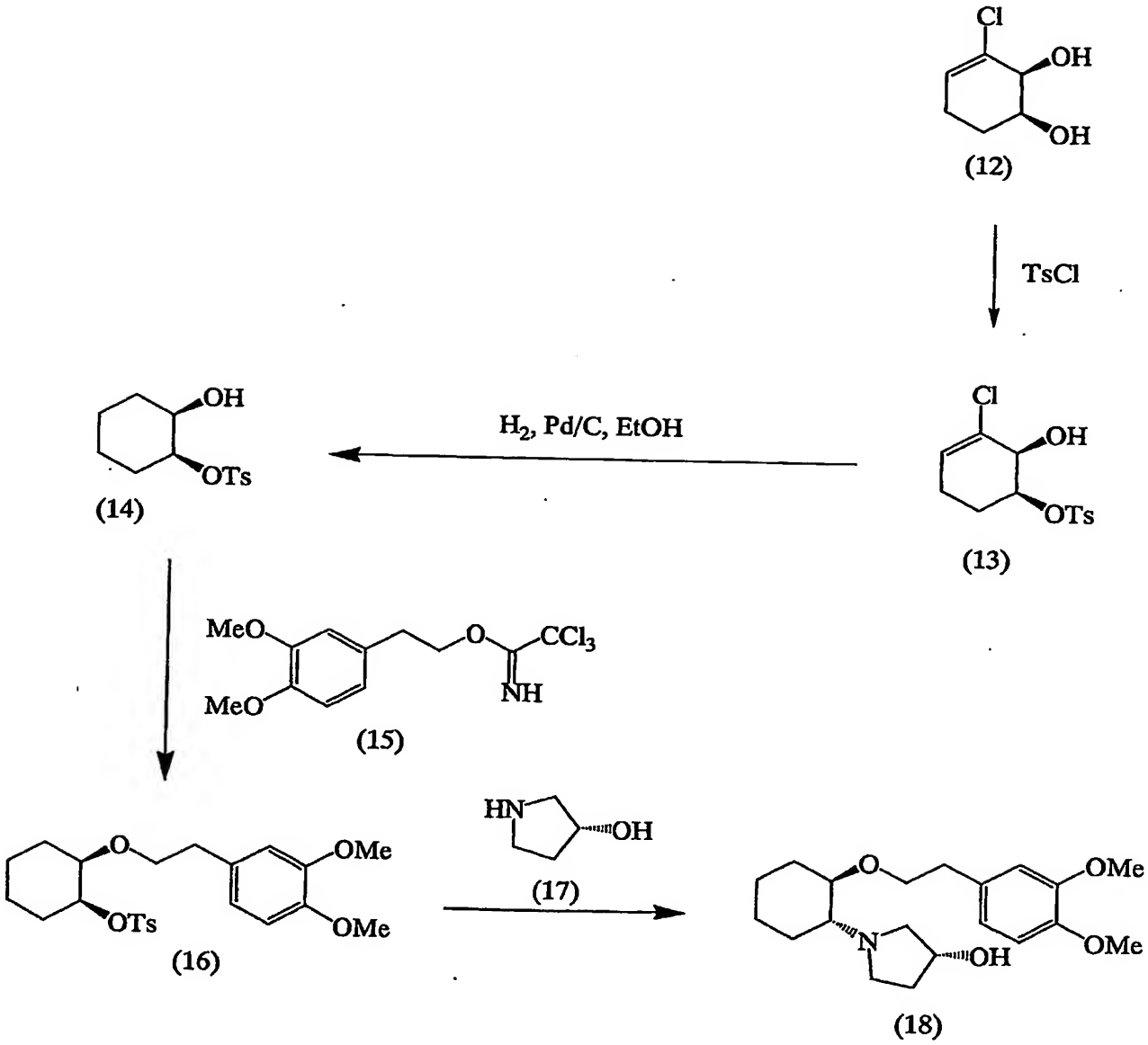
Scheme 6B


Cl
OH
OH
(11)
Rh/Al2O3, H2
Cl
OH
OH
(12)
TsCl
Cl
OH
OTs
(13)
H2, Pd/C, EtOH
OH
OTs
(14)
MeO
MeO
O
CCl3
NH
(15)
O
OMe
OMe
OTs
(16)
HN
OBn
(23)
O
OMe
OMe
N
OBn
(24)
O
OMe
OMe
N
OH
(22)

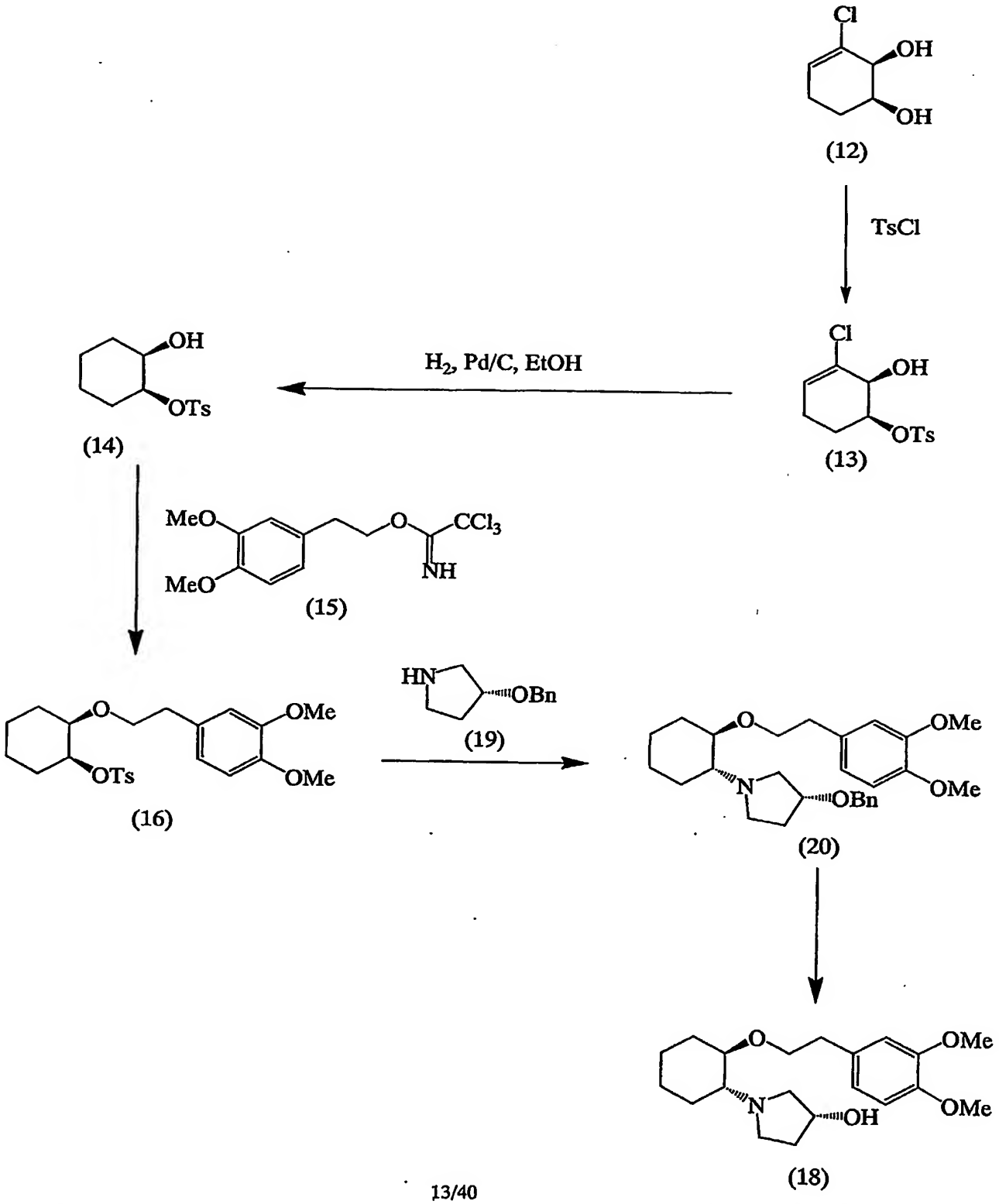
Scheme 7


X
OH
OH
(3)
OH
O—J
(5)
X
OH
O—J
(4)
R3
O
O
Q
R4
R5
(6)
R4
O
R5
O—J
R3
(7)
R1
HN
R2
(8)
R4
O
R5
N
R1
R2
R3
(9)

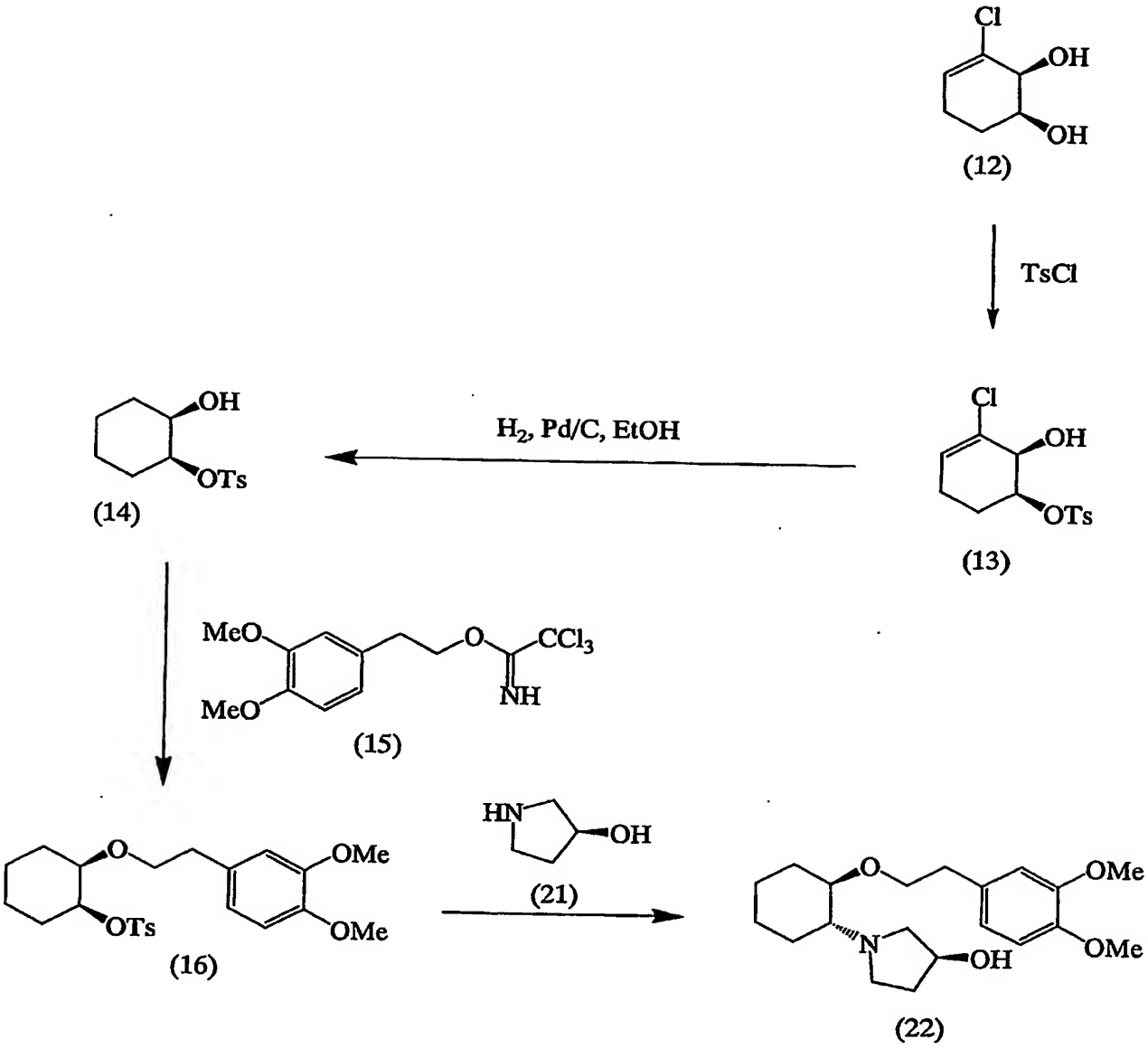
Scheme 8A


Cl
OH
OH
(12)
TsCl
Cl
OH
OTs
(13)
H2, Pd/C, EtOH
OH
OTs
(14)
MeO
MeO
O
CCl3
NH
(15)
HN
OH
(17)
O
OTs
OMe
OMe
(16)
O
N
OH
OMe
OMe
(18)

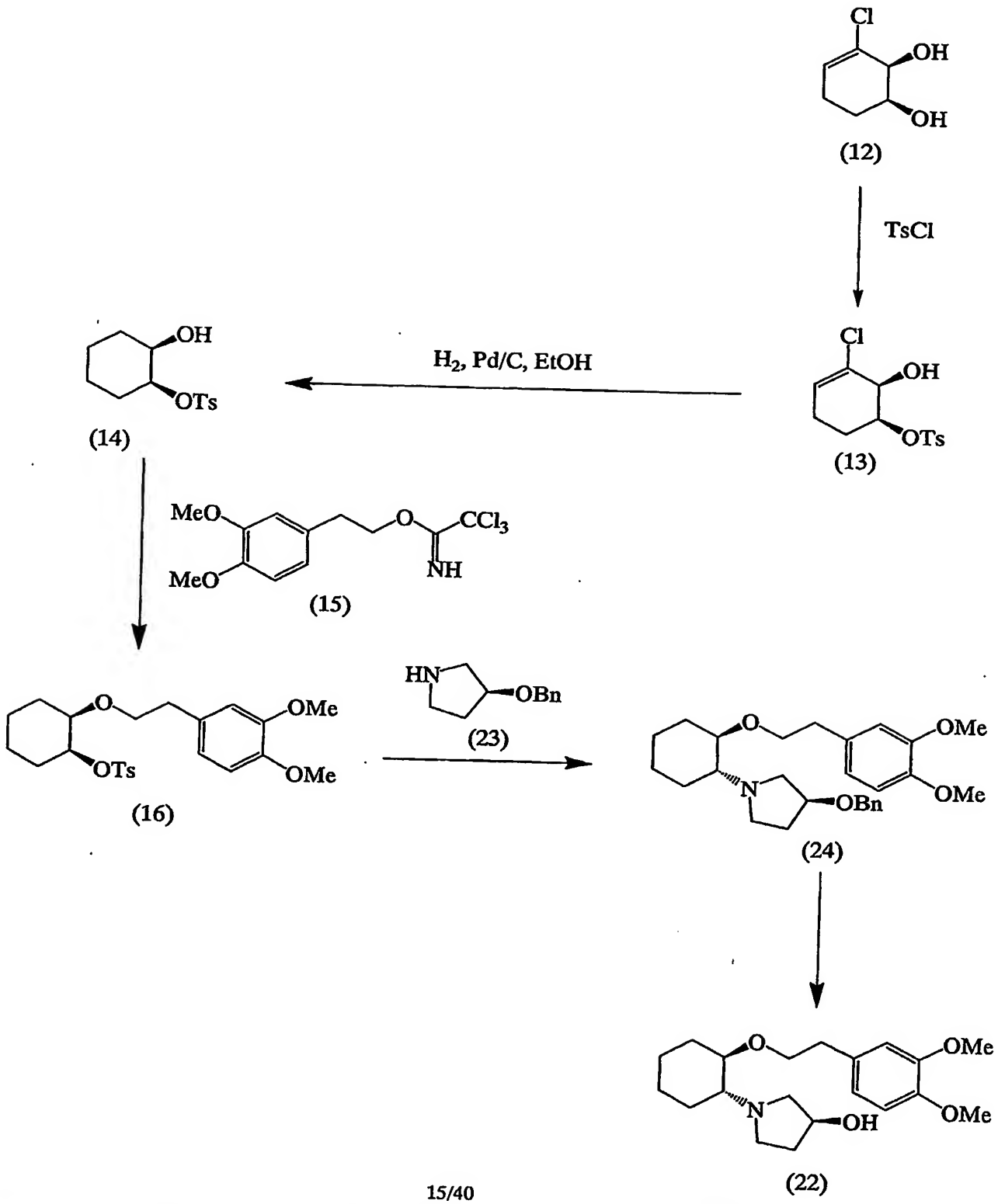
Scheme 8B


Cl
OH
OH
(12)
TsCl
Cl
OH
OTs
(13)
H2, Pd/C, EtOH
OH
OTs
(14)
MeO
MeO
O
CCl3
NH
(15)
HN
OBn
(19)
O
OMe
OTs
OMe
(16)
O
OMe
N
OBn
OMe
(20)
O
OMe
N
OH
OMe
(18)

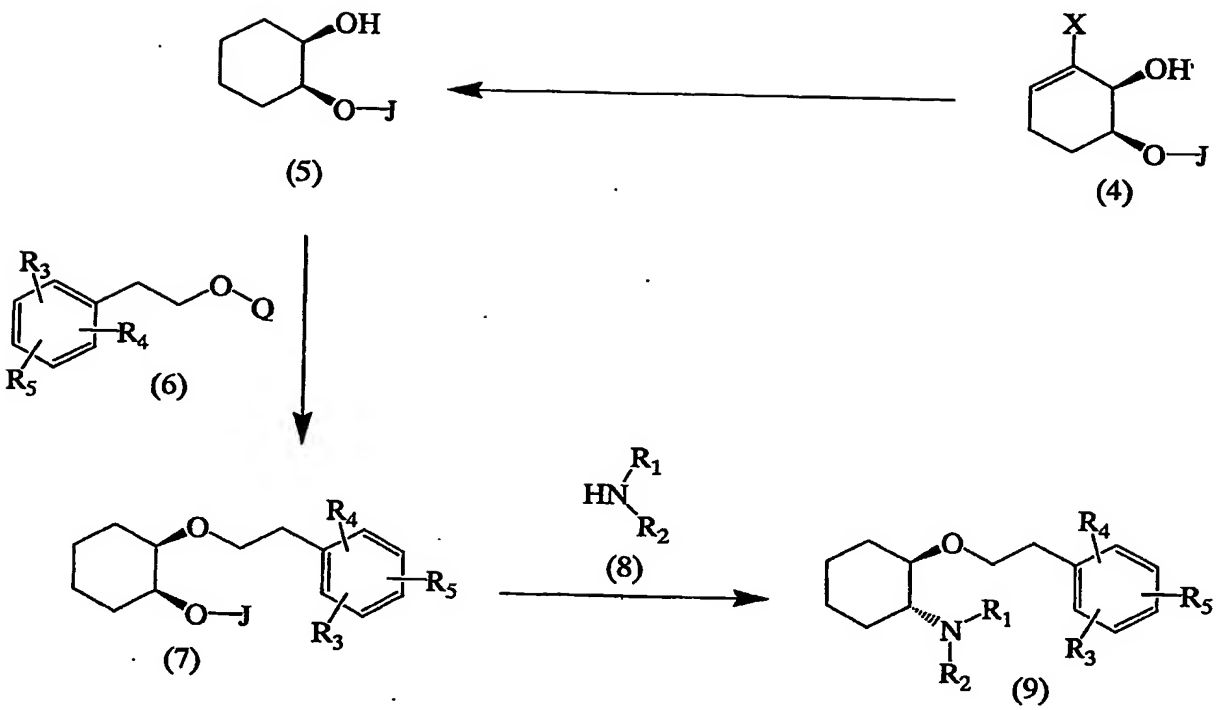
Scheme 9A


Cl
OH
OH
(12)
TsCl
Cl
OH
OTs
(13)
H2, Pd/C, EtOH
OH
OTs
(14)
MeO
MeO
O
CCl3
NH
(15)
O
OTs
OMe
OMe
(16)
HN
OH
(21)
O
N
OH
OMe
OMe
(22)

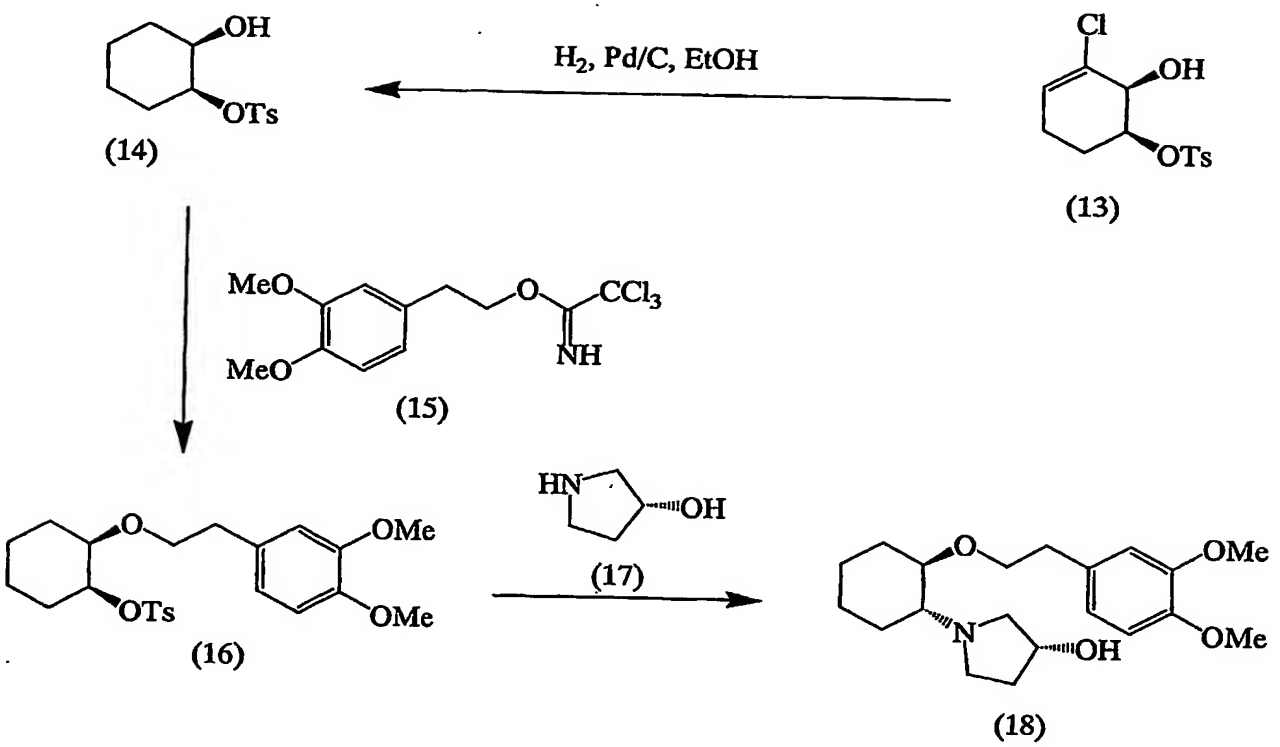
Scheme 9B


Cl
OH
OH
(12)
TsCl
Cl
OH
OTs
(13)
H2, Pd/C, EtOH
OH
OTs
(14)
MeO
MeO
O
CCl3
NH
(15)
O
OMe
OTs
OMe
(16)
HN
OBn
(23)
O
OMe
N
OBn
OMe
(24)
O
OMe
N
OH
OMe
(22)

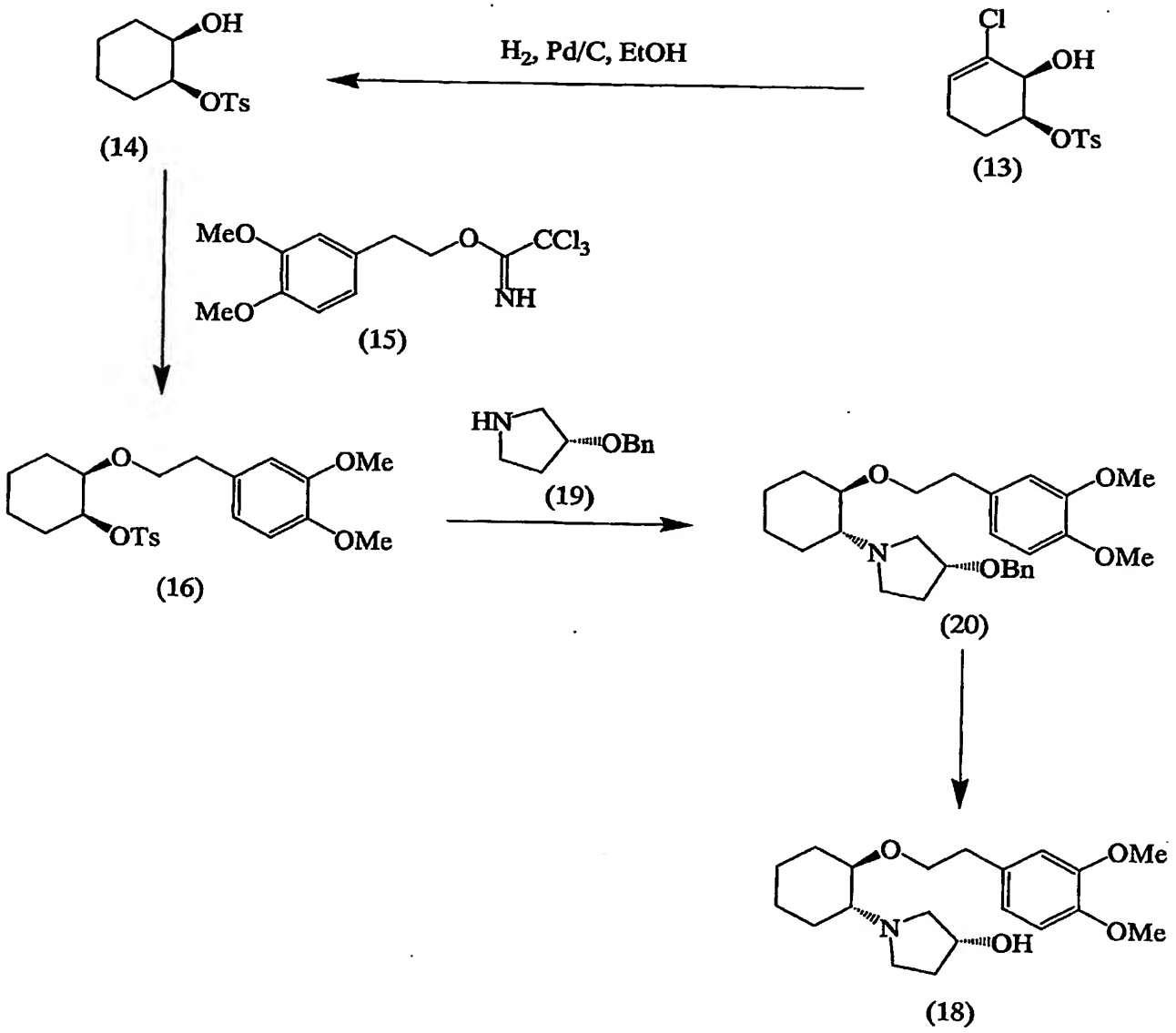
Scheme 10



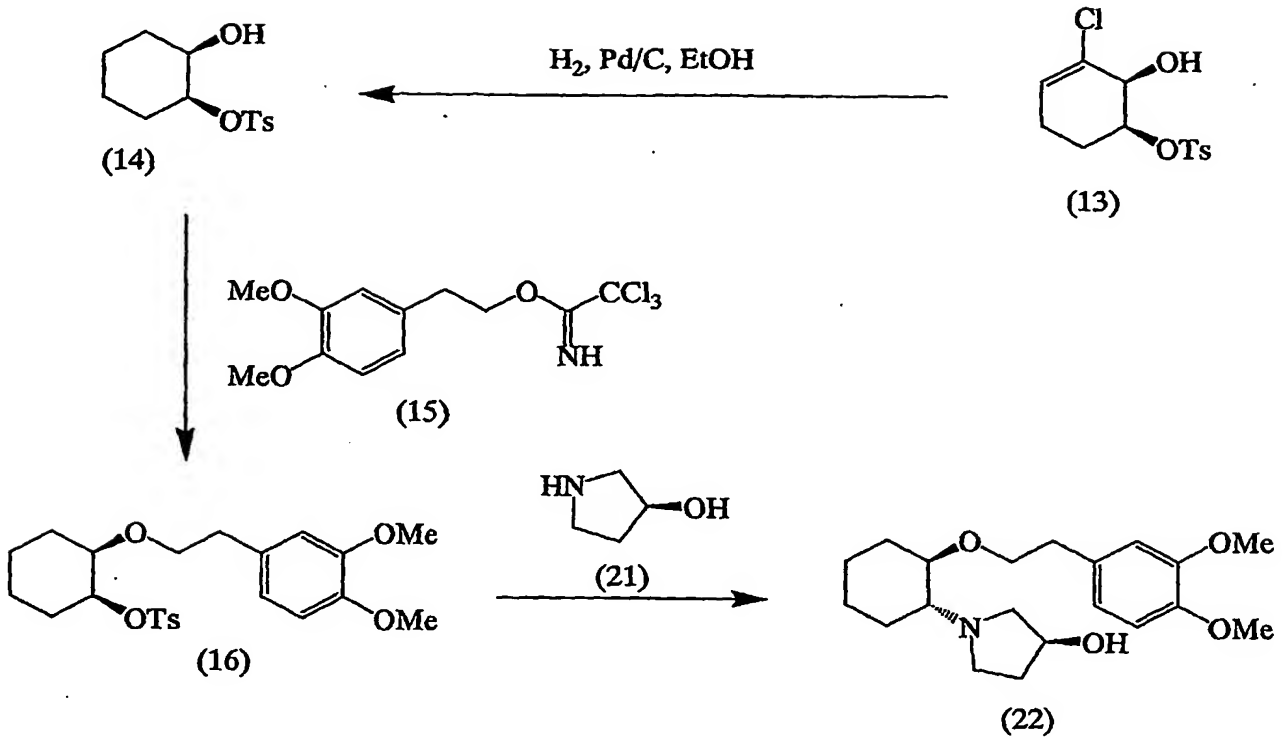
Scheme 11A


OH
OTs
(14)
H2, Pd/C, EtOH
Cl
OH
OTs
(13)
MeO
MeO
O
CCl3
NH
(15)
O
OTs
OMe
OMe
(16)
HN
OH
(17)
O
N
OH
OMe
OMe
(18)

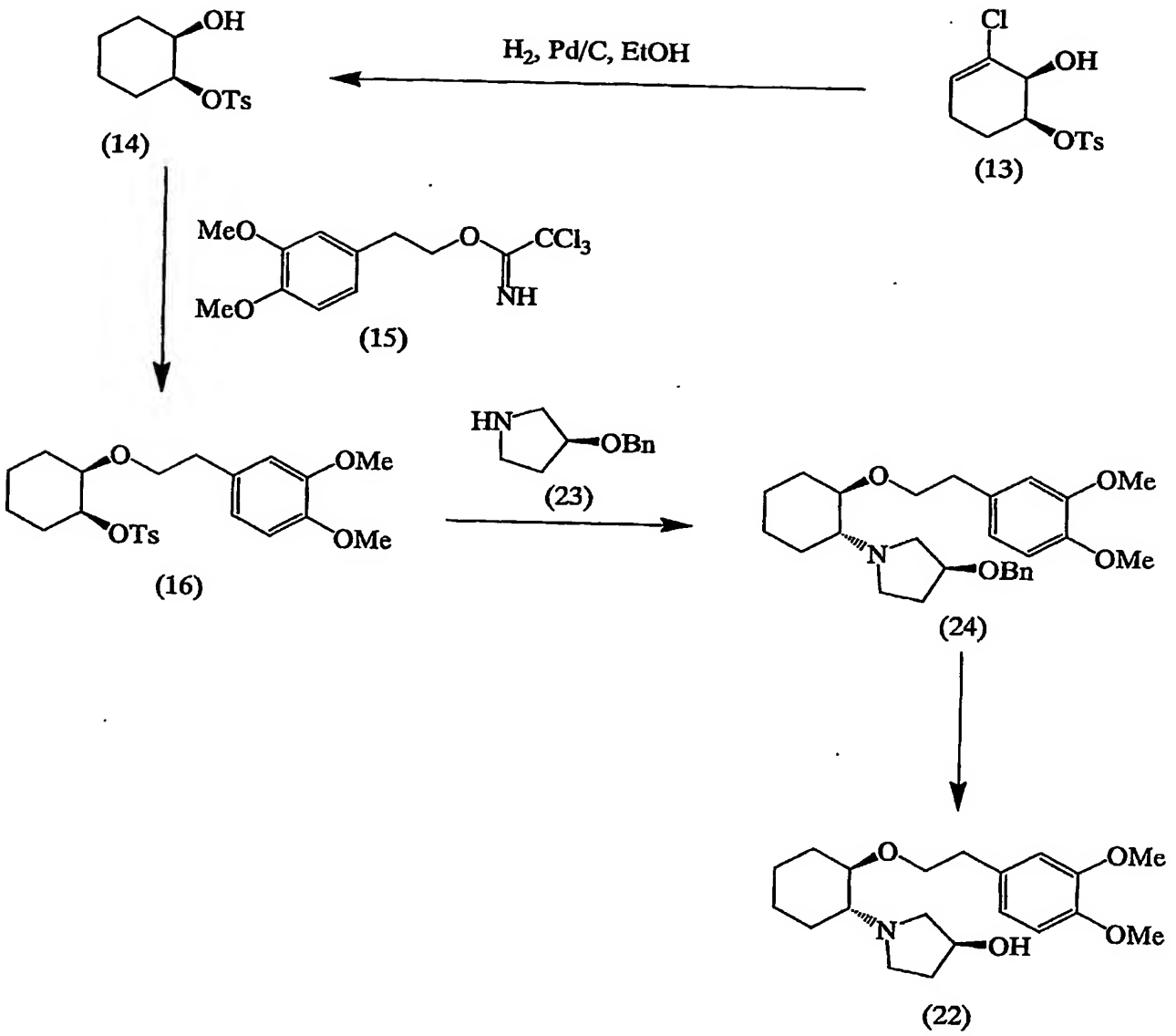
Scheme 11B


OH
OTs
(14)
H2, Pd/C, EtOH
Cl
OH
OTs
(13)
MeO
MeO
O
CCl3
NH
(15)
O
OTs
OMe
OMe
(16)
HN
OBn
(19)
O
N
OBn
OMe
OMe
(20)
O
N
OH
OMe
OMe
(18)

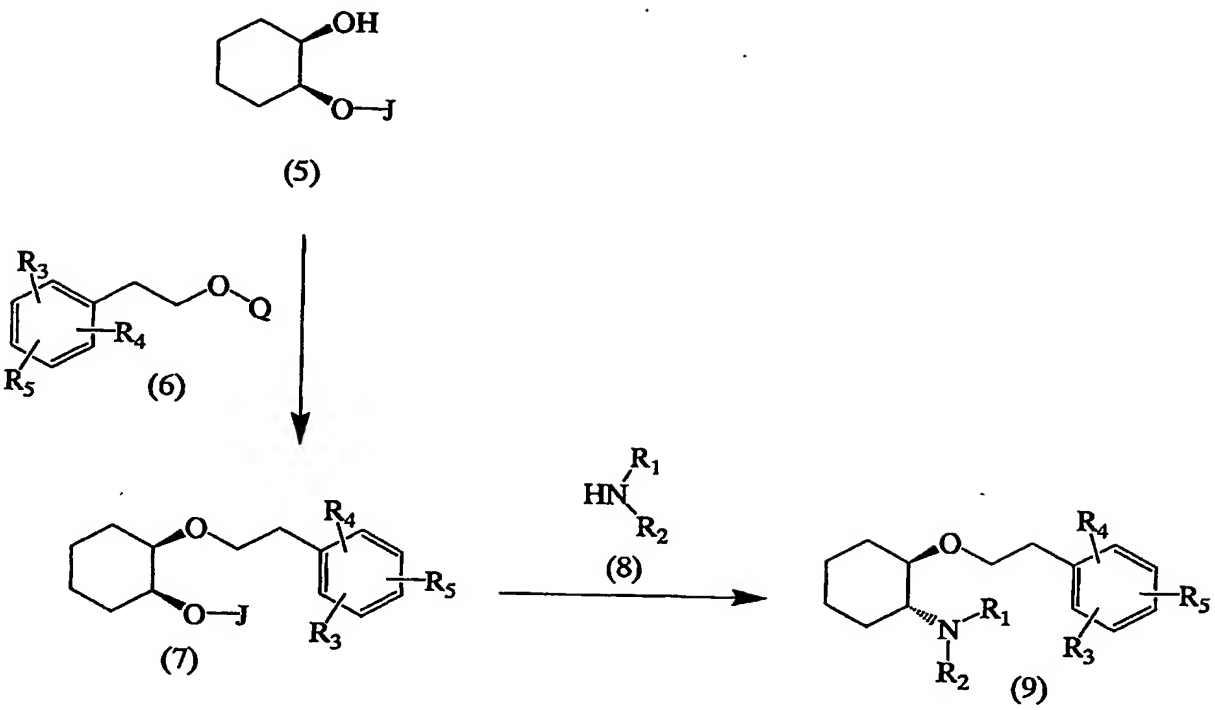
Scheme 12A


OH
OTs
(14)
H2, Pd/C, EtOH
Cl
OH
OTs
(13)
MeO
MeO
O
CCl3
NH
(15)
HN
OH
(21)
O
OMe
OTs
OMe
(16)
O
OMe
N
OH
OMe
(22)

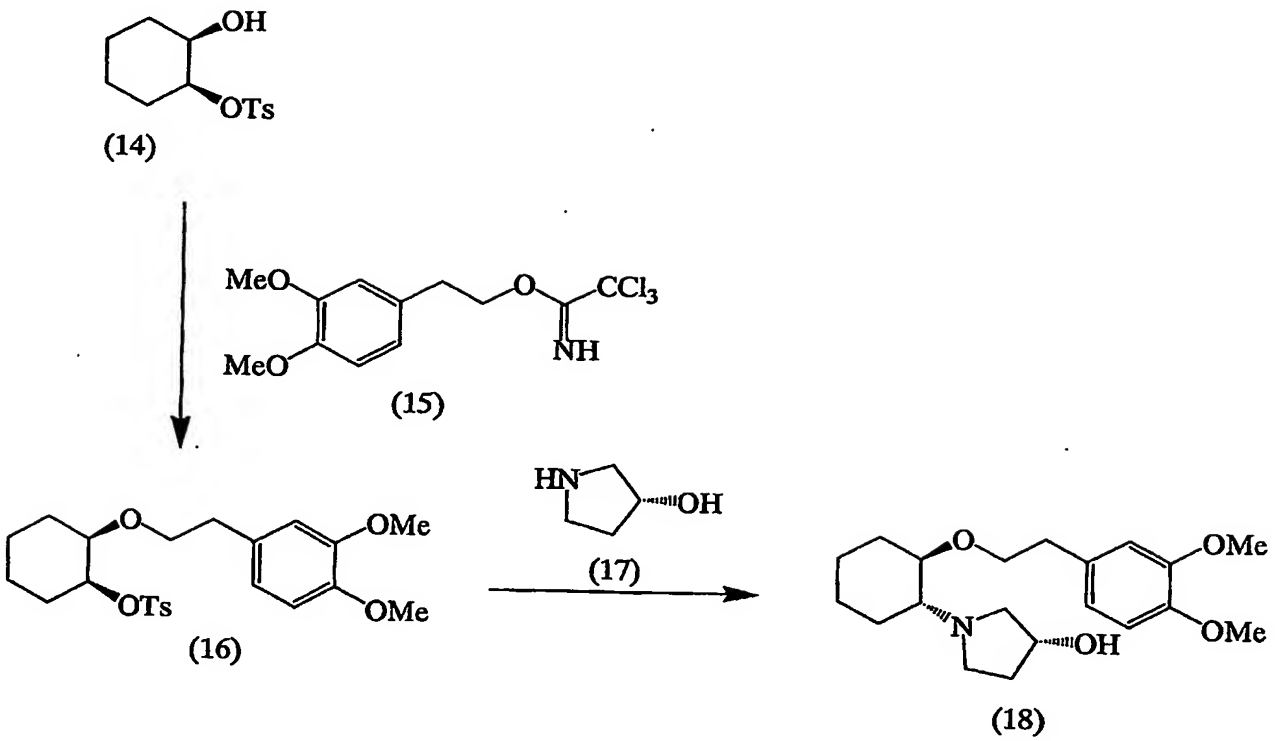
Scheme 12B


OH
OTs
(14)
H2, Pd/C, EtOH
Cl
OH
OTs
(13)
MeO
MeO
O
CCl3
NH
(15)
O
OTs
OMe
OMe
(16)
HN
OBn
(23)
O
N
OBn
OMe
OMe
(24)
O
N
OH
OMe
OMe
(22)

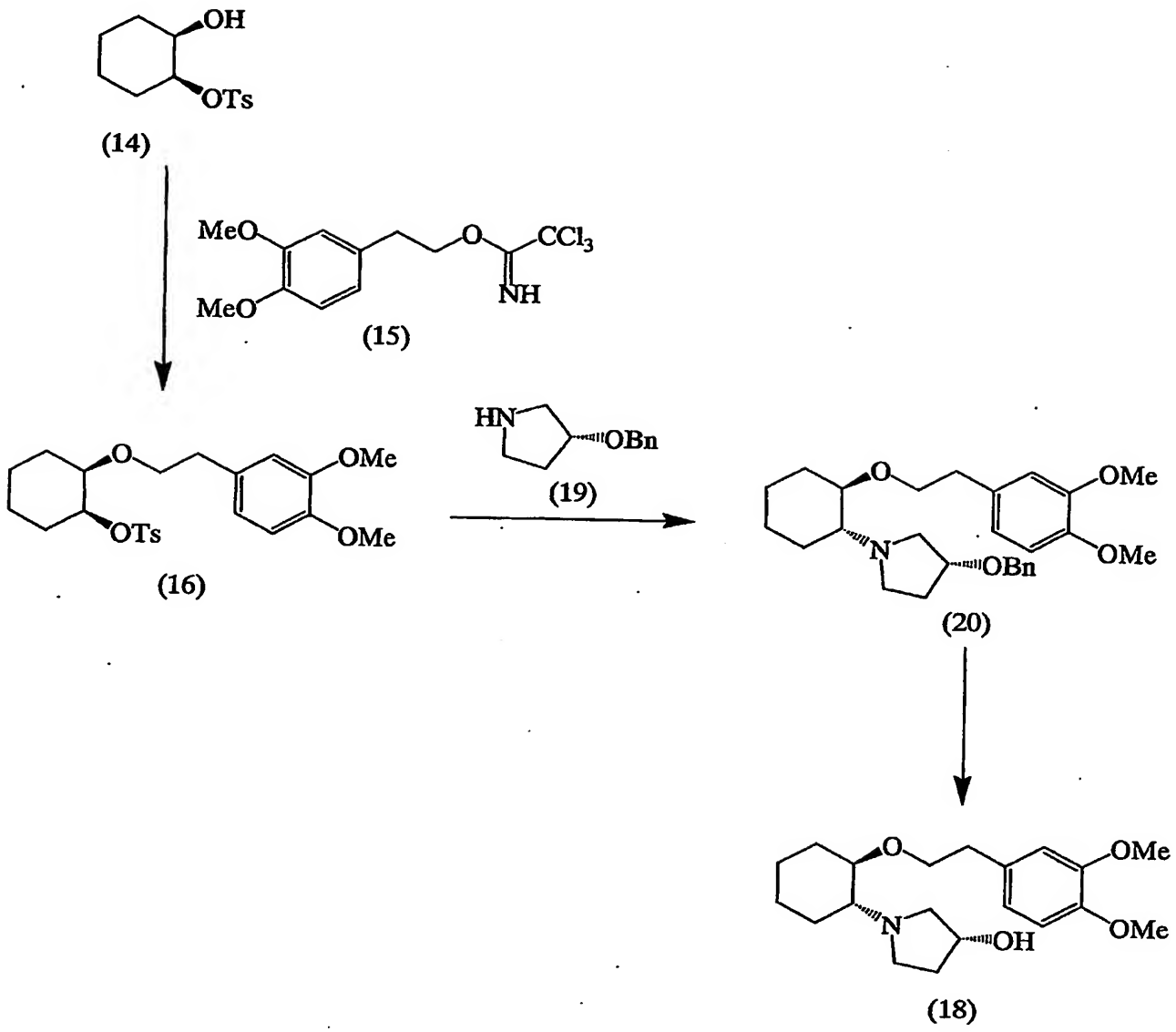
Scheme 13



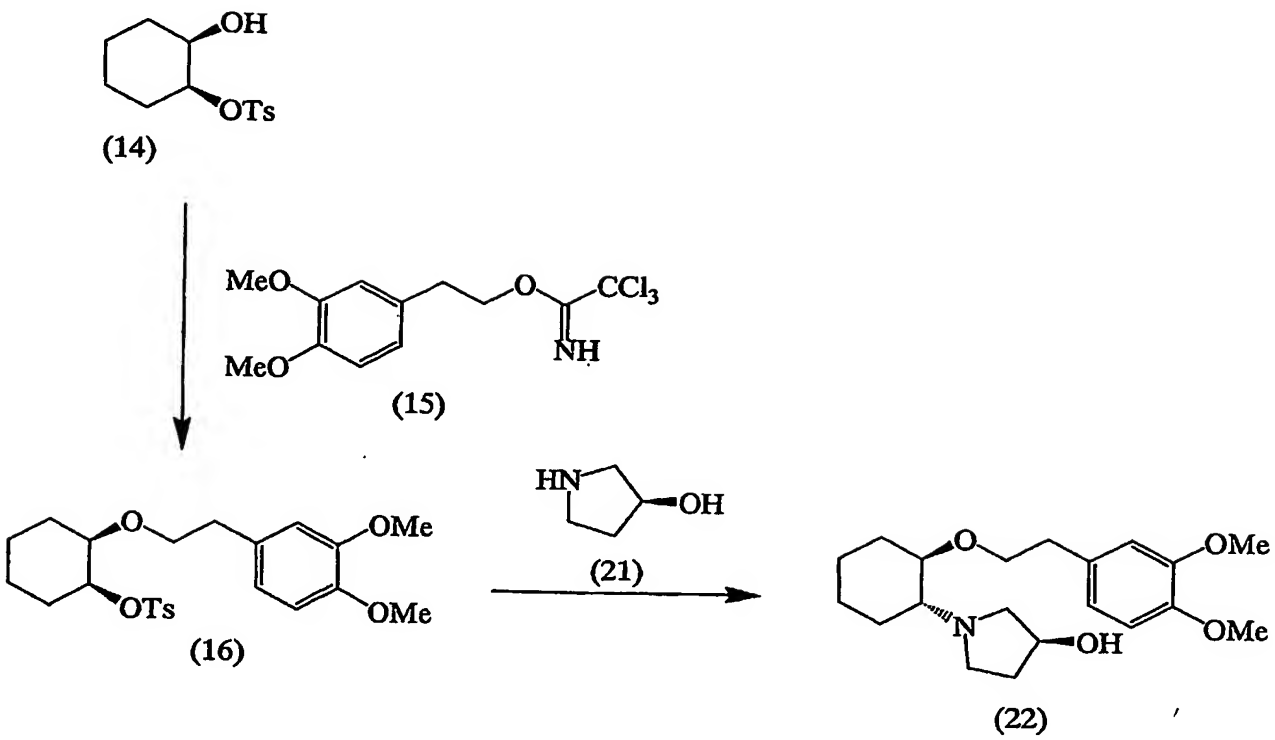
Scheme 14A


OH
OTs
(14)
MeO
MeO
O
CCl3
NH
(15)
O
OMe
OTs
OMe
(16)
HN
OH
(17)
O
OMe
N
OH
OMe
(18)

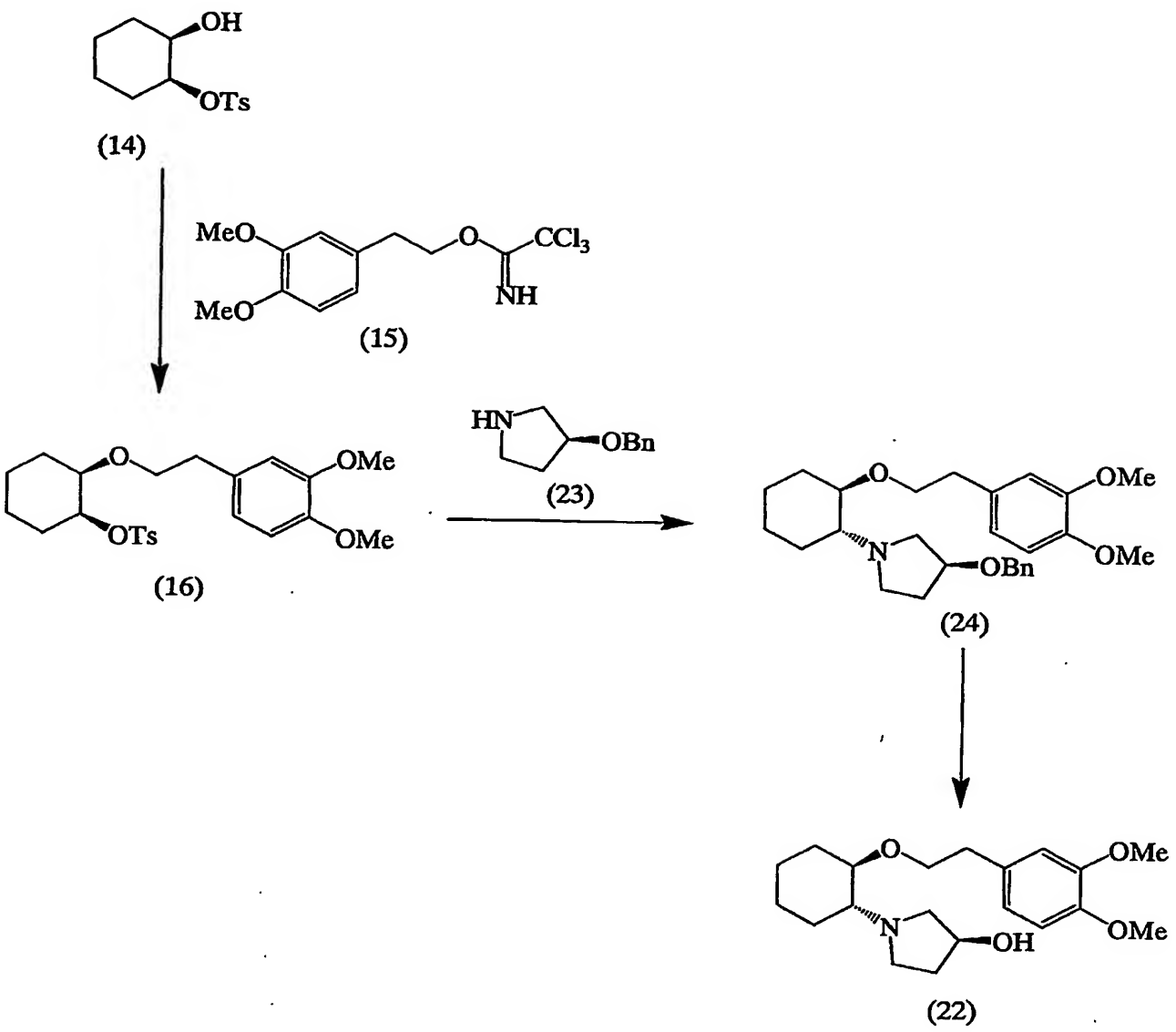
Scheme 14B


OH
OTs
(14)
MeO
MeO
O
CCl3
NH
(15)
HN
OBn
(19)
O
OTs
OMe
OMe
(16)
O
OMe
N
OBn
OMe
(20)
O
OMe
N
OH
OMe
(18)

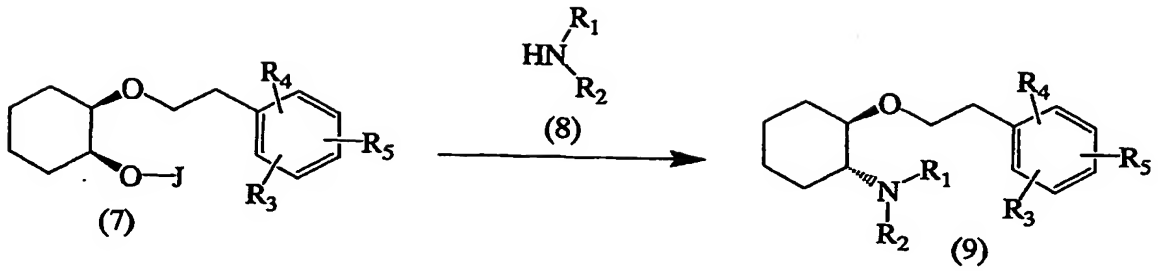
Scheme 15A


OH
OTs
(14)
MeO
MeO
O
CCl3
NH
(15)
O
OTs
OMe
OMe
(16)
HN
OH
(21)
O
N
OH
OMe
OMe
(22)

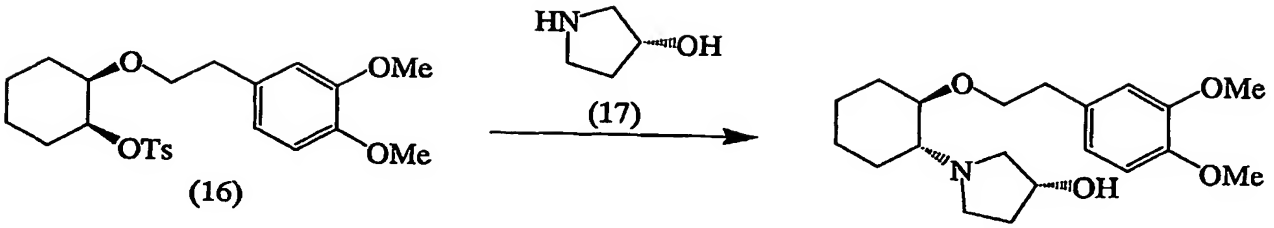
Scheme 15B


OH
OTs
(14)
MeO
MeO
O
CCl3
NH
(15)
O
OTs
OMe
OMe
(16)
HN
OBn
(23)
O
N
OBn
OMe
OMe
(24)
O
N
OH
OMe
OMe
(22)

Scheme 16

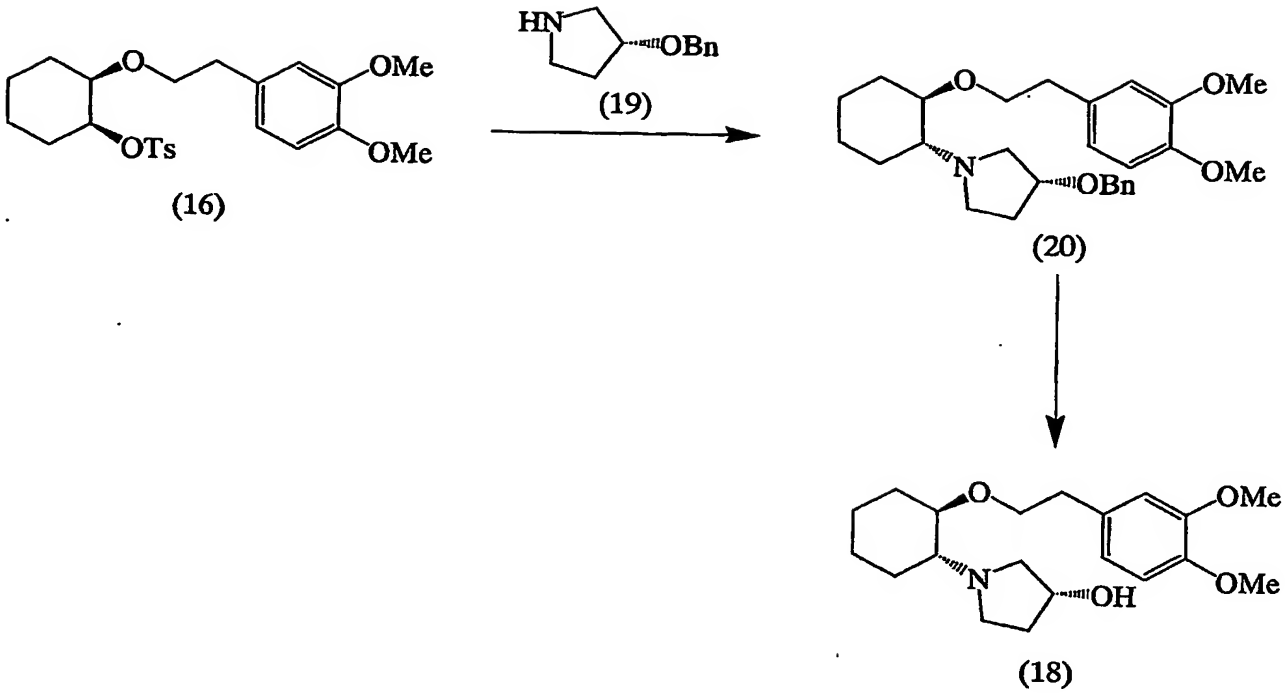


Scheme 17A

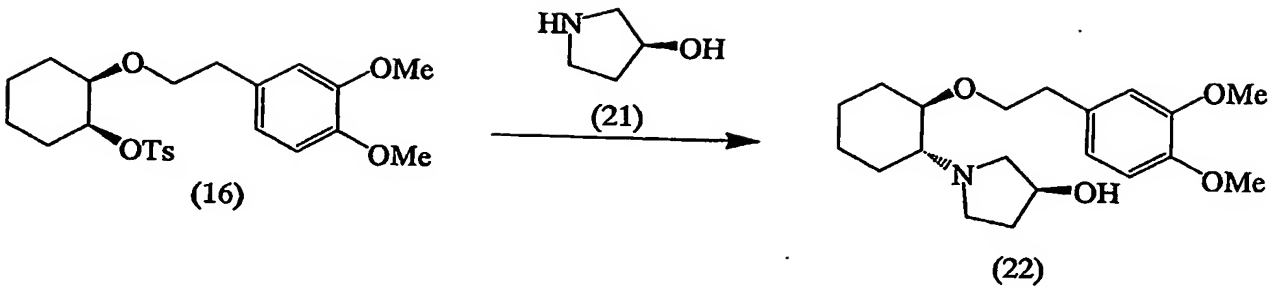


(16) (18)

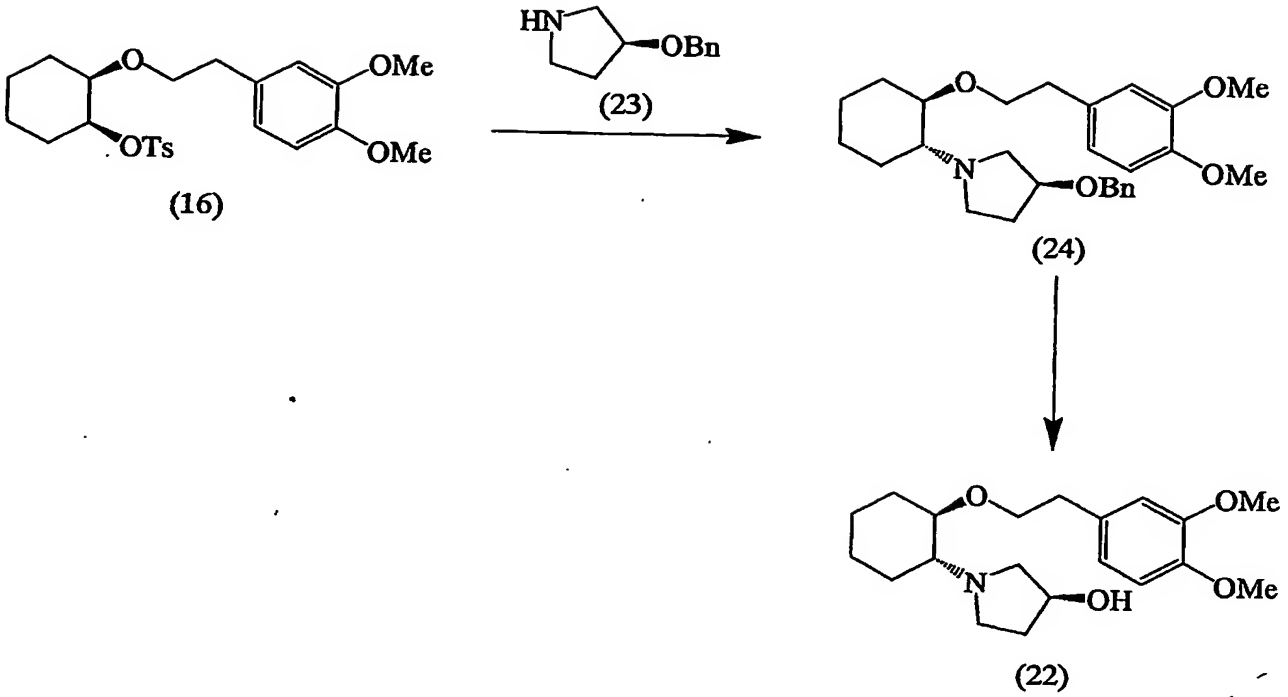
Scheme 17B



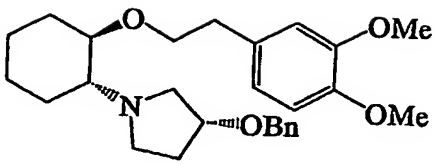
Scheme 18A



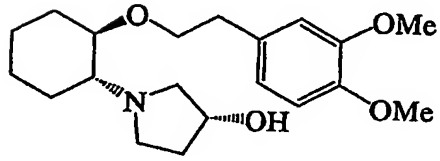
Scheme 18B



Scheme 19B

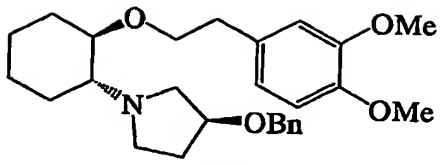


(20)

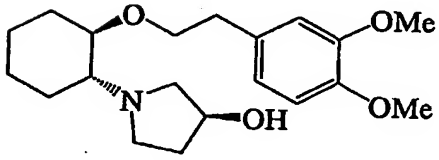


(18)

Scheme 20B

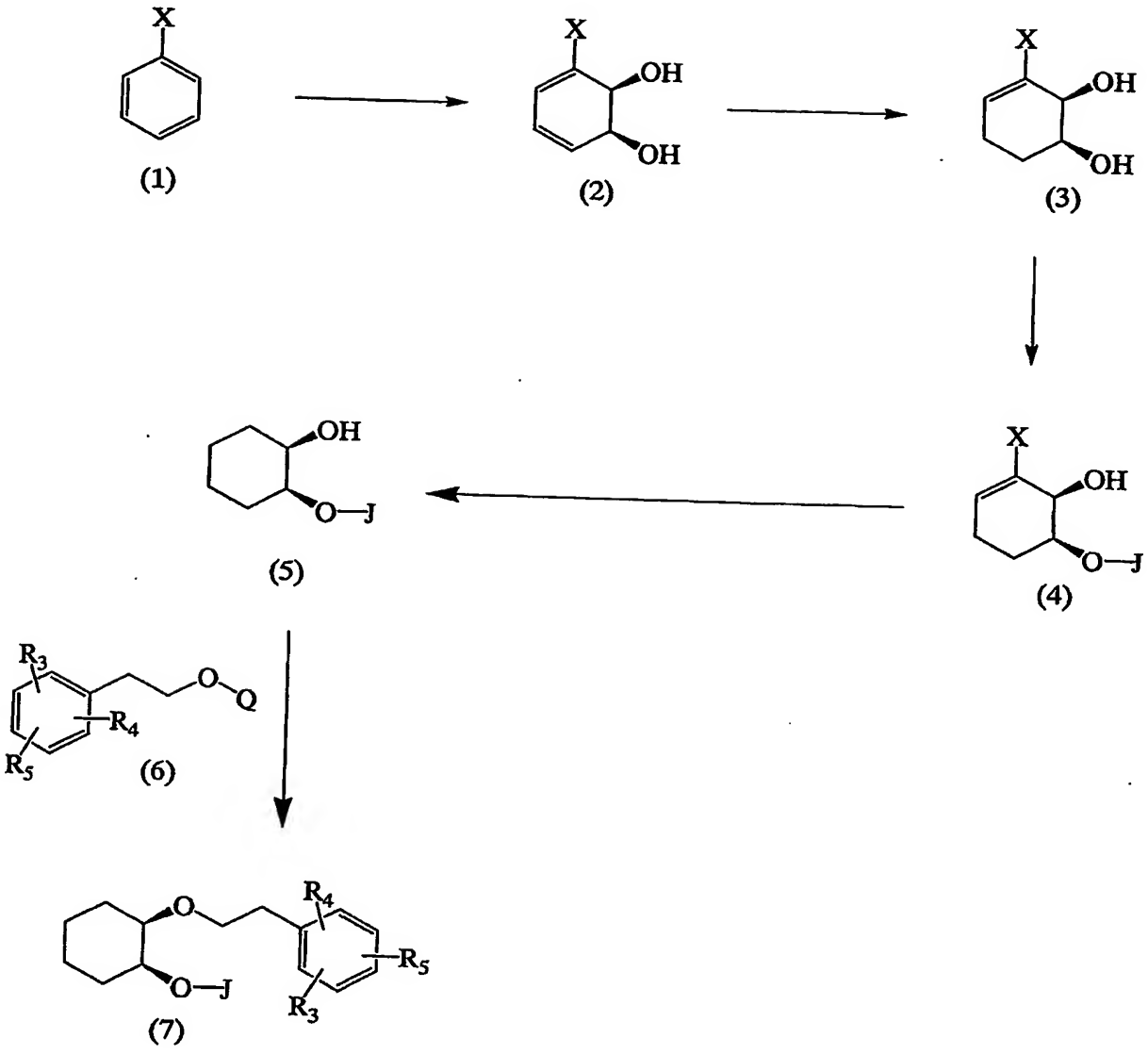


(24)

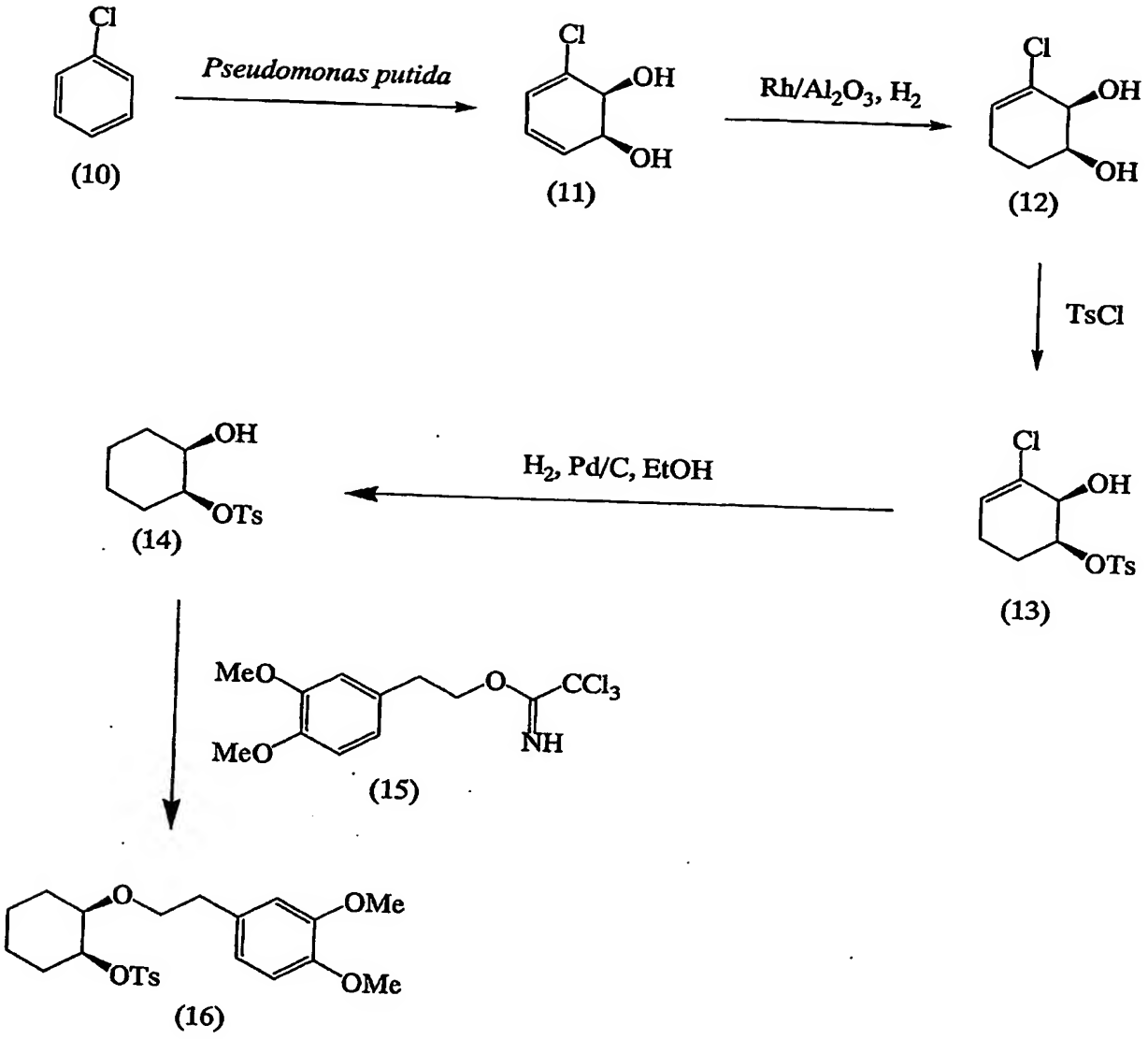


(22)

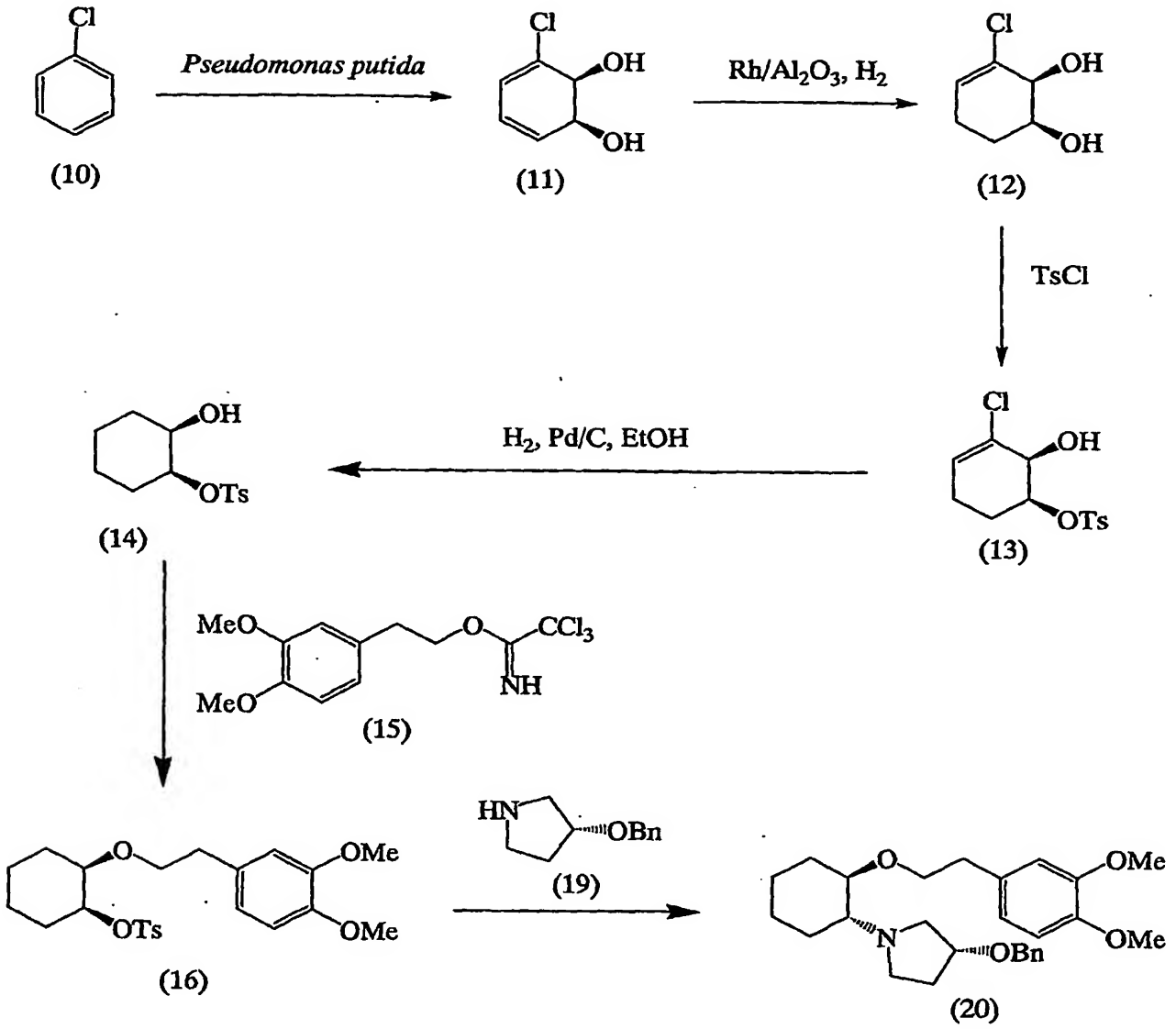
Scheme 21



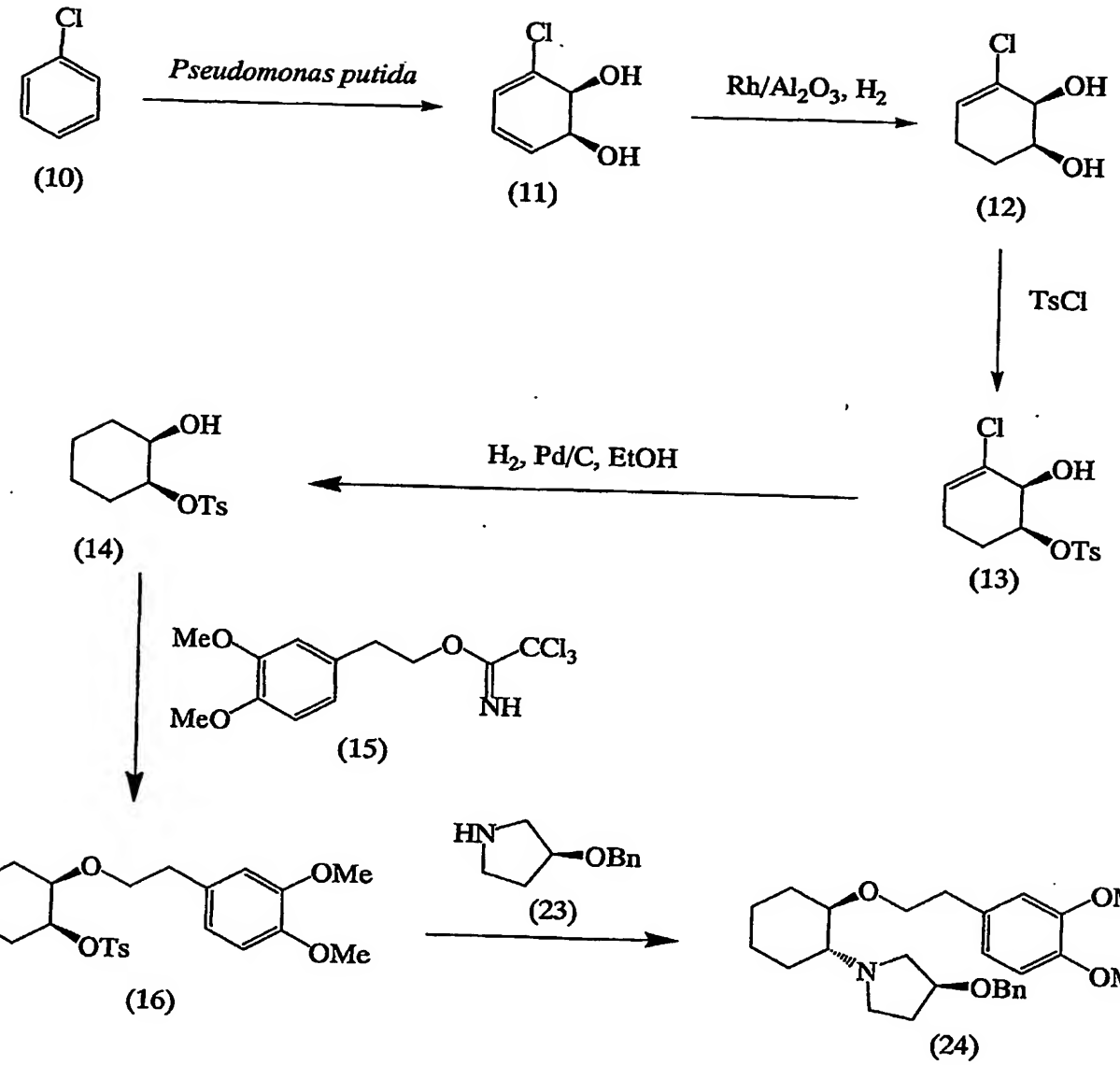
Scheme 22A


Cl
(10)
Pseudomonas putida
Cl
OH
OH
(11)
Rh/Al2O3, H2
Cl
OH
OH
(12)
TsCl
Cl
OH
OTs
(13)
H2, Pd/C, EtOH
OH
OTs
(14)
MeO
MeO
O
CCl3
NH
(15)
O
OTs
OMe
OMe
(16)

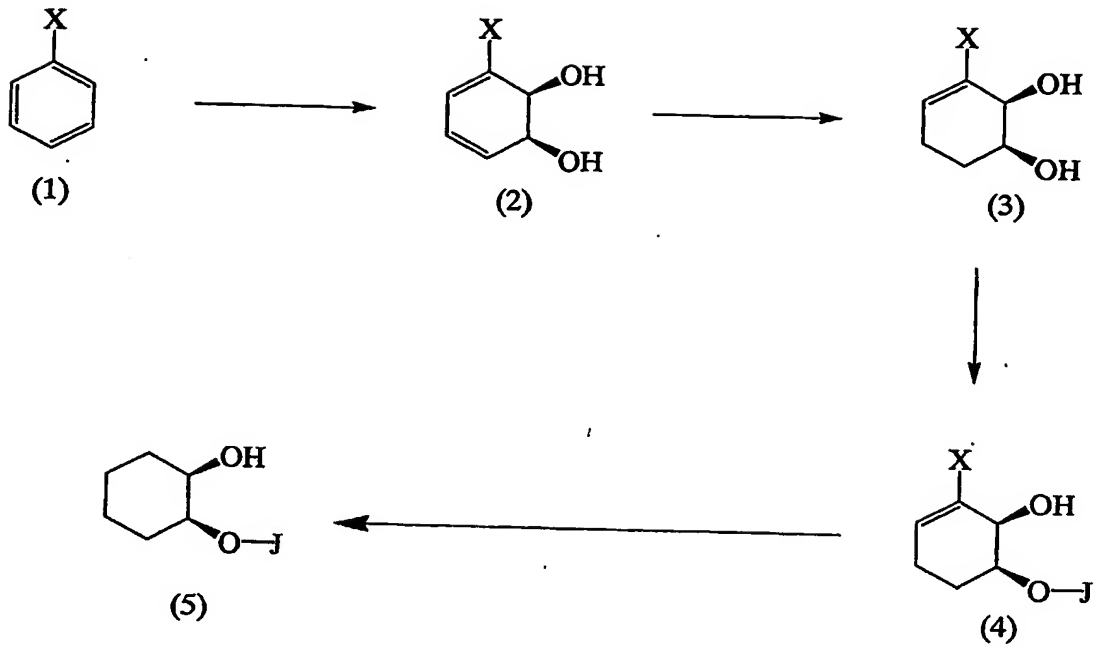
Scheme 22B


Cl
(10)
Pseudomonas putida
Cl
OH
OH
(11)
Rh/Al2O3, H2
Cl
OH
OH
(12)
TsCl
Cl
OH
OTs
(13)
H2, Pd/C, EtOH
OH
OTs
(14)
MeO
MeO
O
CCl3
NH
(15)
HN
OBn
(19)
O
OMe
OTs
OMe
(16)
O
OMe
N
OBn
OMe
(20)

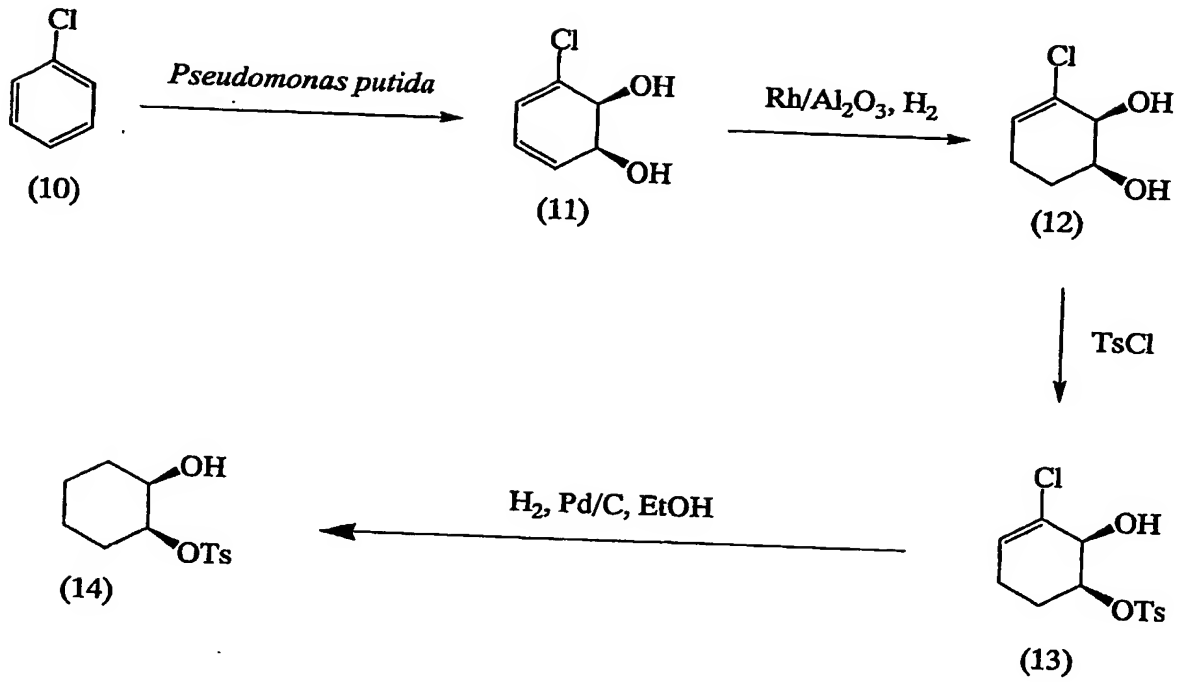
Scheme 23B


Cl
Pseudomonas putida
OH
OH
Rh/Al2O3, H2
TsCl
H2, Pd/C, EtOH
OTs
MeO
MeO
CCl3
NH
HN
OBn
OMe
(10)
(11)
(12)
(13)
(14)
(15)
(16)
(23)
(24)

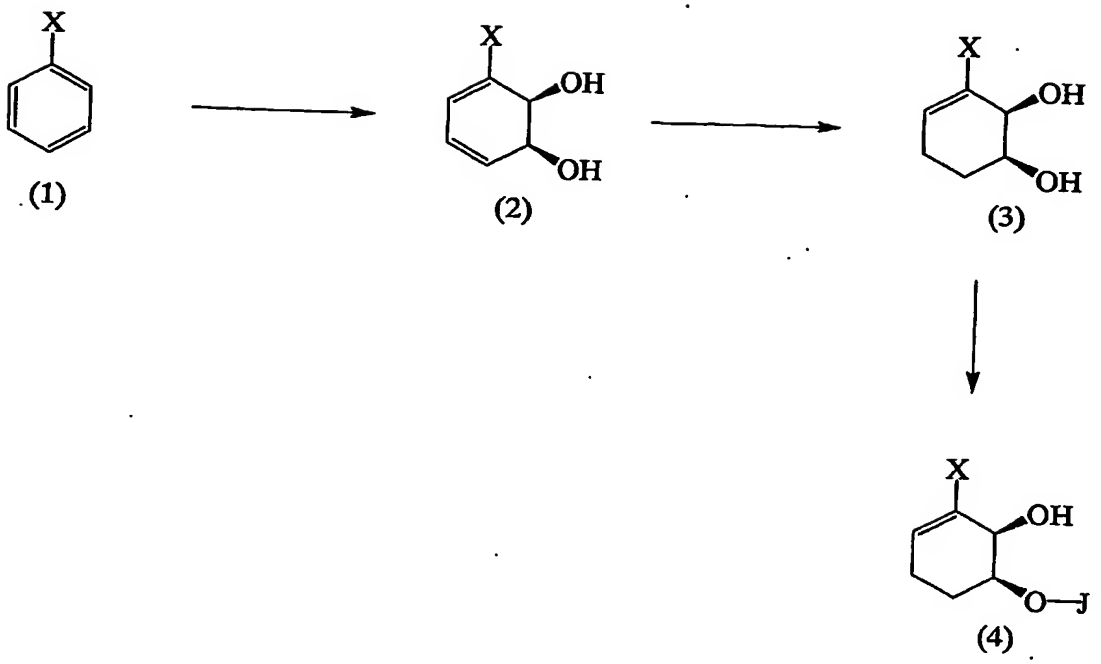
Scheme 24



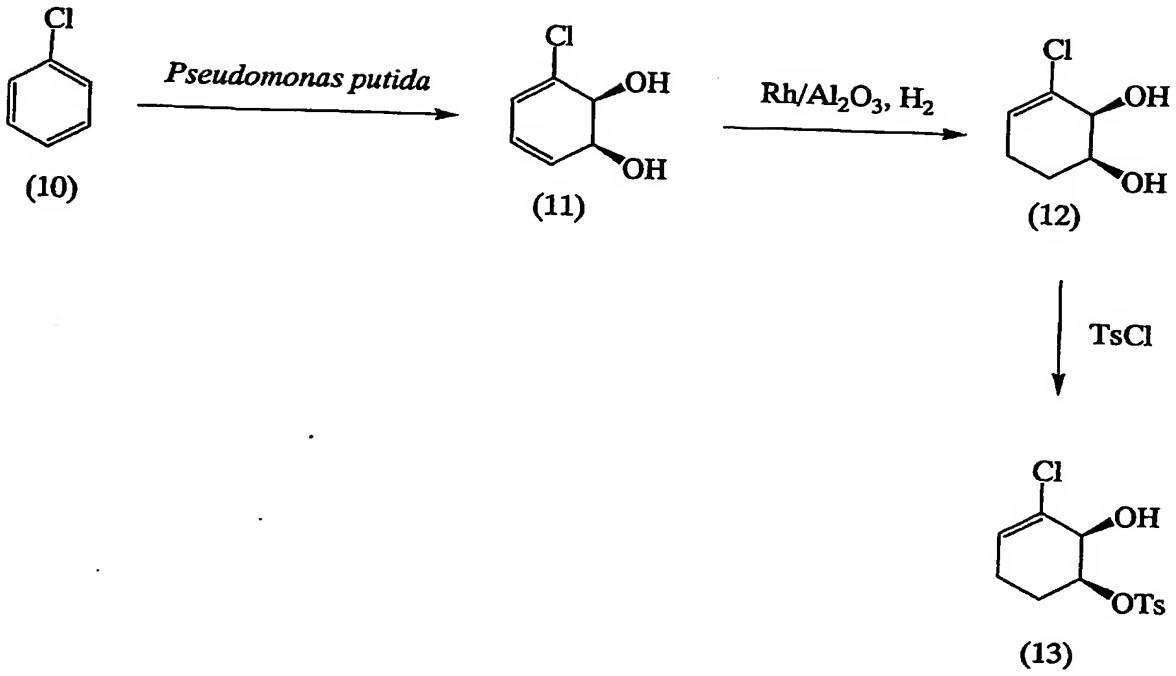
Scheme 25A


Cl
(10)
Pseudomonas putida
Cl
OH
OH
(11)
Rh/Al2O3, H2
Cl
OH
OH
(12)
TsCl
Cl
OH
OTs
(13)
H2, Pd/C, EtOH
OH
OTs
(14)

Scheme 26



Scheme 27A



(10) (11) (12) (13)

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